Government of Canada Gouvernement du Canada

Canada

# Screening Assessment

# Talc
# ($Mg_3H_2(SiO_3)_4$)

## Chemical Abstracts Service Registry Number
## 14807-96-6

## Environment and Climate Change Canada
## Health Canada

## April 2021

Cat. No.: En84-227/2021E-PDF

ISBN 978-0-660-37965-4

Information contained in this publication or product may be reproduced, in part or in whole, and by any means, for personal or public non-commercial purposes, without charge or further permission, unless otherwise specified.

You are asked to:

- Exercise due diligence in ensuring the accuracy of the materials reproduced;
- Indicate both the complete title of the materials reproduced, as well as the author organization; and
- Indicate that the reproduction is a copy of an official work that is published by the Government of Canada and that the reproduction has not been produced in affiliation with or with the endorsement of the Government of Canada.

Commercial reproduction and distribution is prohibited except with written permission from the author. For more information, please contact Environment and Climate Change Canada's Inquiry Centre at 1-800-668-6767 (in Canada only) or 819-997-2800 or email to ec.enviroinfo.ec@canada.ca.

© Her Majesty the Queen in Right of Canada, represented by the Minister of the Environment and Climate Change, 2021.

Aussi disponible en français

# Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of talc. The Chemical Abstracts Service Registry Number (CAS RN[1]) for talc is 14807-96-6. This substance is among those substances identified as priorities for assessment as it met categorization criteria under subsection 73(1) of CEPA.

Talc is a naturally occurring mineral. In 2011, talc was manufactured in Canada in quantities ranging between 50 to 75 million kg, and in 2016, approximately 100 million kg of talc was imported into Canada. In Canada, talc is used in adhesives and sealants; automotive, aircraft, and transportation applications; building and construction materials; ceramics; electrical and electronics; textiles; floor coverings; inks, toners, and colourants; lubricants and greases; oil and natural gas extraction applications; paints and coatings; paper and paper products, mixtures, and manufactured items; plastic and rubber materials; toys, playground equipment and sporting equipment; and in water treatment. The major uses in Canada align with major global uses of talc. Talc is a permitted food additive and is an ingredient in self-care products. In North America, approximately 2% to 4% of the talc produced and sold is used in cosmetics. High-purity talc is used in self-care products including cosmetics, while lower-grade talc is used in commercial applications.

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I), which is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard characterization in ERC-I included a survey of published predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of new PNEC values when required. Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model for each substance and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. Modelled and measured predicted environmental concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment. Based on the outcome of the ERC-I analysis, talc is considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is a low risk of harm to the environment from talc. It is concluded that talc does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is not entering the

[1] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society, and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior written permission of the American Chemical Society.

environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Talc has been reviewed internationally by other organizations, including the International Agency for Research on Cancer (IARC) and the Danish Environmental Protection Agency. These assessments informed the human health risk assessment.

No critical health effects were identified via the oral or dermal routes of exposure. As such, oral exposure to talc resulting from food intake and oral and dermal exposure from the use of self-care products are not of concern. Inhalation exposure via ambient air for the general population from industrial and commercial uses of talc was not identified to be of concern for human health given the limited number of sites producing and processing talc in Canada. Rather, the focus of the assessment is on inhalation and perineal exposure to certain self-care products containing cosmetic- or pharmaceutical-grade talc.

With respect to inhalation exposure, non-cancer lung effects (e.g., inflammation, impaired lung function, fibrosis) were identified as a critical health effect for risk characterization on the basis of United States National Toxicology Program studies conducted with rats and mice exposed to cosmetic-grade talc. There is potential for inhalation exposure to talc powder during the use of certain self-care products (e.g., cosmetics, natural health products, non-prescription drugs formulated as loose powders). Self-care products formulated as pressed powders (e.g., face makeup) are not of concern for inhalation exposure. Margins of exposure between air concentrations following the use of dry hair shampoo and foot powder and critical lung effects observed in animal studies are considered adequate to address uncertainties in the health effects and exposure databases. Margins of exposure between air concentrations following the use of body powder, baby powder, and loose face powder and critical lung effect levels observed in animal studies are considered potentially inadequate to address uncertainties in the health effects and exposure databases.

With regards to perineal exposure, analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. The available data are indicative of a causal effect. Given that there is potential for perineal exposure to talc from the use of certain self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs, bubble bath), a potential concern for human health has been identified.

Considering all the information presented in this screening assessment, it is concluded that talc meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that talc meets one of the criteria set out in section 64 of CEPA. It has also been determined that talc meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

# Table of Contents



# List of Tables

# 1. Introduction

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of talc to determine whether this substance presents or may present a risk to the environment or to human health. This substance was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA (ECCC, HC [modified 2017]).

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) (ECCC 2018), which is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard characterization in ERC-I included a survey of published predicted no-effect concentrations (PNECs) and water quality guidelines, or the derivation of a new PNEC value when required. Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model for each substance and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. Modelled and measured predicted environmental concentrations (PECs) were compared to PNECs, and multiple statistical metrics were computed and compared to decision criteria to classify the potential for causing harm to the environment.

With respect to human health, this screening assessment includes the consideration of information on chemical properties, environmental fate, hazards, uses, and exposures, including additional information submitted by stakeholders. Relevant data were identified up to October 2020. Empirical data from key studies, as well as results from models, were used to reach conclusions. Talc has been reviewed internationally through the International Agency for Research on Cancer (IARC) Monographs Programme, the United States Environmental Protection Agency (U.S. EPA), the Joint Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) Expert Committee on Food Additives (JECFA), and the Danish Environmental Protection Agency (Danish EPA). Talc was also assessed by the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission) in Germany and the Cosmetic Ingredient Review (CIR) Expert Panel.[2] These evaluations and reviews were used to inform the health effects characterization in this screening assessment. This assessment focuses on health effects associated with cosmetic- and pharmaceutical-

[2] The Cosmetic Ingredient Review was established in 1976 by the industry trade association (then the Cosmetic, Toiletry, and Fragrance Association, now the Personal Care Products Council), with the support of the U.S. Food and Drug Administration and the Consumer Federation of America.

grade talc and not on potential impurities, such as asbestos. Engineered nanomaterials composed of or containing talc are not explicitly considered in this assessment.

This screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and in the Consumer and Hazardous Products Safety Directorate at Health Canada and incorporates input from other programs within these departments. Health Canada scientists conducted research to characterize airborne particles emitted during application of cosmetic talc products (Rasmussen et al. 2019). This peer-reviewed published research has informed the assessment. The ecological portion of the assessment is based on the ERC-I (published May 11, 2018), which was subject to an external peer review and a 60-day public comment period. The human health portion of this assessment has undergone external peer review. Comments on the technical portions relevant to human health were received from T. Lopez, MSPH, K. Super, DABT, and Z. Jeney, MPH, of Tetra Tech. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. Additional information submitted during the public comment period was reviewed and considered for the final screening assessment. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution.[3] This screening assessment presents the critical information and considerations on which the conclusion is based.

## 2. Identity of substance

Talc (CAS RN[4] 14807-96-6) is one of the softest naturally occurring minerals, made up of magnesium, silicon, hydrogen and oxygen (ChemIDplus 1993- ). The term talc refers

[3] A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion on the basis of the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

[4] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior written permission of the American Chemical Society.

to both the pure mineral and a wide variety of soft, talc-containing rocks that are mined and used for a variety of applications (Kogel et al. 2006). Relatively pure talc ore is also referred to as steatite, and soapstone refers to impure, massive talc rock (Fiume et al. 2015).

The mineral talc is composed of triple-sheet crystalline units, consisting of two silicate sheets composed of $SiO_4$ tetrahedra joined by edge-linked $MgO_4(OH)_2$ (Zazenski et al. 1995). These layers, held together loosely via van der Waals forces, slide over one another easily, giving talc its slippery feel and accounting for its softness (Fiume et al. 2015). The size of an individual talc platelet (i.e., a few thousand elementary sheets) can vary from approximately 1 µm to over 100 µm, depending on the conditions of formation of the deposit (EuroTalc 2017). The individual platelet size determines the lamellarity of a sample of talc. Highly lamellar talc will have large individual platelets, whereas microcrystalline talc will have small platelets. Other inorganics in place of magnesium and silicon are common in talc; for example, aluminum and iron may substitute for silicon in the tetrahedral sites, or manganese may substitute for magnesium in the octahedral positions (Zazenski et al. 1995).

Commercially exploited talc contains 20% to 99% of the pure mineral (Kogel et al. 2006). Some of the most common minerals that occur with talc are carbonates (e.g., dolomite, calcite, magnesite) and chlorite (i.e., magnesium aluminum silicate) (CIR 2013). Less common minerals include quartz, mica, iron oxides, pyrite, serpentine, and amphibole. Selective mining, ore processing, and beneficiation can remove many of the impurities (Kogel et al. 2006). There is a trend towards upgrading to higher-purity talc; however, many applications require the properties of the minerals associated with talc (Kogel et al. 2006) and the purity of the source talc influences its uses.

There are different grades of talc that refer to the purity (presence of other minerals). Pharmaceutical-grade talc complies with the United States Pharmacopeia (USP) standards (or similar standards), which require the absence of asbestos and set limits on iron, lead, calcium, and aluminum (USP 2011). As per B.01.045 of the *Food and Drug Regulations*, when used as a food additive, talc must meet the food-grade specifications set out in with the most recent edition of the *Food Chemicals Codex*, published by the United States Pharmacopeial Convention or the *Combined Compendium of Food Additive Specifications*, prepared by the Joint FAO/WHO Expert Committee on Food Additives, and must be free from asbestos (Canada [1978]; FAO 2006; FCC 2016).

Historically, some talc source materials were contaminated with asbestos. However, in 1976, the Cosmetic Toiletry and Fragrance Association (CTFA) set purity standards for cosmetic-grade talc resulting in a reduction in asbestos levels in cosmetic products (Fiume et al. 2015). Cosmetic-grade talc should comply with USP standards that require a limit of 20 ppm lead and an absence of asbestos (Fiume et al. 2015). Currently the USP standard for talc is under review (USP 2019; USP 2020a, USP b) and the United States Food and Drug Administration (U.S. FDA) is working on recommendations on

testing methods for asbestos in talc and products available to consumers containing talc (U.S. FDA 2020a). Internationally, a number of regulatory agencies continue to conduct testing on talc-based cosmetic products for the presence of asbestos (NVWA 2018; U.S. FDA 2020b).

In Canada, the *Prohibition of Asbestos and Products Containing Asbestos Regulations* (updated 2018) under CEPA prohibit asbestos above trace levels in products available to consumers, including cosmetics. The cosmetic-grade talc used in the health effect studies cited in this assessment were considered to be free of asbestos.[5]

Talc is milled to different particle sizes for specific commercial applications. Most talc for cosmetics and pharmaceuticals is pure 200-mesh roller-milled talc (Kogel et al. 2006). In 200-mesh talc (preferred for body powder and deodorants), the particle size distribution allows 95% to 99% of the product to pass through a 200-mesh (74 µm) screen (Zazenski et al. 1995; Kogel et al. 2006). The finer 325-mesh talc is also used in cosmetic-, pharmaceutical-, and food-grade formulations, where 95% to 99% of the product passes through a 325-mesh (44 µm) screen.

# 3. Physical and chemical properties

A summary of physical and chemical properties of talc is presented in Table 3-1. Talc is a chemically inert, solid powder that is insoluble in water (Kogel et al. 2006, EuroTalc 2017).

**Table 3-1. Experimental physical and chemical property values (at standard temperature) for talc**

| Property | Range | Key reference |
|---|---|---|
| Physical state | solid, powder | HSDB 2005 |
| Melting point (°C) | 1500 | EuroTalc 2017 |
| Vapour pressure (mm Hg) | approx. 0, negligible at 20°C | OSHA 1999; NIOSH 2014 |
| Water solubility (mg/L) | Insoluble | HSDB 2005 |
| Specific gravity (unitless) | 2.58–3.83 | HSDB 2005 |

# 4. Sources and uses

Talc is a naturally occurring mineral, and there are talc deposits in most Canadian provinces (Kogel et al. 2006). Currently, there is one producing mine (open-pit) and

[5] met the USP standards for absence of asbestos

concentrator facility in Canada, in Penhorwood Township near Timmins, Ontario, and one micronizing facility in Timmins (Kogel et al. 2006; MAC 2019; NPRI 2018). The talc ore from the mine is approximately 45% pure, with magnesite, magnetite, chlorite, and serpentine as the major impurities (Kogel et al. 2006). After beneficiation, this mine and micronizing facility produces talc primarily for the paper, plastics, paint, and ceramic sectors (Kogel et al. 2006). In 2019, China was the largest producer of talc, followed by India and Brazil (USGS 2020). The major uses of talc globally include paper, plastics, paint, ceramics, putties, and cosmetics (USGS 2000; Kogel et al. 2006; EuroTalc 2017; USGS 2020).

Talc was included in a survey issued pursuant to a CEPA section 71 notice. Talc was reported to be manufactured in Canada at quantities ranging from 50 to 75 million kg in 2011 (EC 2013).[6] According to the Canadian International Merchandise Trade (CIMT) database, in 2016, 99 549 000 kg of natural steatite and talc, crushed or powdered (Harmonized System, HS code 252620) and 4 656 000 kg of natural steatite and talc, not crushed, not powdered (HS code 252610) were imported into Canada (CIMT 2017).

According to information submitted in response to a CEPA section 71 survey (EC 2013), results from voluntary stakeholder engagement (ECCC, HC 2017), and a search of websites from talc producers, manufactured or imported talc is used in Canada in adhesives and sealants; automotive, aircraft, and transportation applications; building and construction materials (e.g., wood and engineered wood); ceramics; electrical and electronics; textiles; floor coverings; inks, toners, and colourants; lubricants and greases; oil and natural gas extraction applications; paints and coatings; paper and paper products, mixtures, or manufactured items; plastic and rubber materials; toys, playground equipment and sporting equipment; and in water treatment.

Talc is a formulant in pest control products registered in Canada (Health Canada 2010; personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the Risk Management Bureau, Health Canada, dated March 29, 2017; unreferenced).

Additionally, in Canada talc is on the *List of Permitted Food Additives with Other Accepted Uses* (List 8) for limited uses in a small number of foods (Health Canada [modified 2020]). Talc can be used as a coating agent on dried legumes and rice and as a filler and dusting powder for chewing gum as per the *List of Permitted Food Additives with Other Accepted Uses*, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. It may be used as a component in

[6] Values reflect quantities reported in response to the survey conducted under section 71 of CEPA (EC 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

the manufacture of food packaging materials and as a component in incidental additives[7] used in food processing establishments with no food contact (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 31, 2017; unreferenced).

Talc is present in approximately 10 000 self-care products.[8] It is used as a non-medicinal ingredient in approximately 1700 marketed or approved human and veterinary drug products in Canada, including approximately 150 non-prescription drugs (email from the Natural and Non-Prescription Health Products Directorate, Health Canada, to the Risk Management Bureau, Health Canada, dated November 18, 2020; unreferenced). Talc is listed in the Natural Health Products Ingredients Database (NHPID) with a medicinal role and classified as a natural health product substance falling under item 7 (a mineral) of Schedule 1 to the *Natural Health Products Regulations*, as well as with a non-medicinal role for use as abrasive, absorbent, anticaking agent, anticoagulant, base, bulking agent, coating agent, colour additive, diluent, filler, flow enhancer, glidant, lubricant, opacifying agent, or slip modifier (NHPID [modified 2019]). Talc is listed in the Diaper Rash Products Monograph as a permitted medicinal ingredient in diaper rash products in concentrations ranging from 45% to 100% (Health Canada 2018). However, there are no diaper rash products listed in the Licensed Natural Health Products Database (LNHPD) containing talc as a medicinal ingredient (LNHPD [modified 2018]). Talc is permitted as a medicinal ingredient in the Traditional Chinese Medicine Ingredients monograph (Health Canada 2015). Talc is listed in the LNHPD as being present as a medicinal or non-medicinal ingredient in approximately 2100 currently licensed NHPs in Canada (LNHPD [modified 2018]).

Based on notifications submitted from 2017 to 2020 under the *Cosmetic Regulations* to Health Canada, talc is an ingredient in approximately 7750 cosmetic products in Canada (personal communication, emails from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 27, 2020; unreferenced). Talc is considered a restricted ingredient in cosmetics.[9] The Cosmetic Ingredient Hotlist entry for cosmetics

[7] While not defined under the Food and Drugs Act (FDA), incidental additives may be regarded, for administrative purposes, as those substances that are used in food processing plants and that may potentially become adventitious residues in foods (e.g., cleaners, sanitizers).

[8] Self-care products are products available for purchase without a prescription from a doctor and fall into one of three broad categories: cosmetics, natural health products, and non-prescription drugs.

[9] Talc is described as a restricted ingredient on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances may contravene the general prohibition found in section 16 of the *Food and Drugs Act* (FDA) or may contravene one or more provisions of the

containing talc in powder form intended to be used on infants and children indicates that product labels should display statements to the effect of “keep out of reach of children” and “keep powder away from child’s face to avoid inhalation which can cause breathing problems.” As per the Cosmetic Regulations, the label of a cosmetic that presents an avoidable hazard must include directions for safe use, in both English and French.

High-purity talc is used in self-care products, while lower-grade talc is used in the many commercial applications mentioned above. Approximately 2% to 4% of the talc produced and sold in North America is used in cosmetics (Kogel et al. 2006; USGS 2020).

Condoms and medical gloves are regulated as Class II medical devices in Canada under the *Medical Devices Regulations* and may be sources of exposure if talc is present as a dry lubricant. However, internationally, there was a shift from the use of talc as a dry lubricant on medical patient examination gloves to cornstarch in the 1980s (Lundberg et al. 1997). In 2016, the U.S. FDA banned powdered patient examination gloves (United States 2016). There has also been a shift from the use of talc as a dry lubricant in condoms, and starch is more commonly used (Douglas et al. 1998). A 1998 study did not find talc in a small survey of condoms tested in Canada (Douglas et al. 1998). Condom standards and specifications require the use of dry lubricants, if present, to be bioabsorbable, such as starch and calcium carbonate; talc should not be used (Douglas et al. 1998; WHO, UNFPA, FHI 2013).

# 5. Environmental fate and behaviour

## 5.1 Environmental persistence

Talc is considered persistent because it is an insoluble mineral with environmental stability on geological timescales (Bricker et al. 1973). Persistence was also evaluated using read-across with synthetic amorphous silicates. Silica and silicates are expected to be resistant to photodegradation, chemical degradation and biodegradation due to their inorganic structure and the high stability of Si-O bonds (OECD 2004).

## 5.2 Potential for bioaccumulation

Bioaccumulation potential data for talc are lacking for ecological receptors. However, due to talc’s low water solubility and absence of lipophilicity, bioaccumulation of talc in ecological receptors is not anticipated. Talc may be retained in lung tissue of mammals (Danish EPA 2016), but inhalation of significant quantities of talc is an unlikely exposure

*Cosmetic Regulations*. Section 16 of the FDA states that "no person shall sell any cosmetic that has in or on it any substance that may cause injury to the health of the user." In addition, the Hotlist includes certain substances that may make it unlikely for a product to be classified as a cosmetic under the FDA (Health Canada [modified 2018]).

scenario for ecological receptors. Bioaccumulation potential was further evaluated using read-across with synthetic amorphous silicates. Silica can be actively accumulated by some organisms (e.g., some terrestrial plants and diatoms). However, the bioaccumulation potential of silica and silicates is low because of the capacity of organisms to excrete $SiO_2$ components and the absence of lipophilicity in these substances (OECD 2004). There is currently no evidence to suggest that silica and silicates or talc bioaccumulate to harmful levels in the environment.

# 6. Potential to cause ecological harm

## 6.1 Characterization of ecological risk

The ecological risk of talc was characterized using the Ecological Risk Classification of Inorganic Substances (ERC-I) (ECCC 2018), which is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard characterization in ERC-I included a survey of published PNECs and water quality guidelines from domestic and international assessments. When no suitable existing PNEC or water quality guideline was found, hazard endpoint data were collected and, depending on data availability, either a species sensitivity distribution (SSD) or an assessment factor (AF) approach was taken to derive a new PNEC value. In the case of talc, hazard endpoint data from the Organisation for Economic Co-operation and Development Screening Information Dataset (SIDS) for synthetic amorphous silicates (OECD 2004) were identified for read-across (ECCC, HC 2017) and an AF approach was used to derive a PNEC value of 40 mg/L (ECCC 2018).

Exposure profiling in ERC-I considered two approaches: predictive modelling using a generic near-field exposure model and an analysis of measured concentrations collected by federal and provincial water quality monitoring programs. The generic near-field exposure model used input data, when available, from the National Pollutant Release Inventory (NPRI), information submitted in response to CEPA section 71 surveys, international trade data from the Canada Border Services Agency (CBSA), and third-party market research reports to generate PECs. For talc, only information submitted in response to a CEPA section 71 survey and international trade data from CBSA were available to generate PECs. Engineered nanomaterials containing talc are not explicitly considered in the exposure scenarios of this assessment but may have been included in the quantities reported.

Modelled PECs were compared to the PNEC, and statistical metrics that consider both the frequency and magnitude of exceedances were computed and compared to decision criteria to classify the potential for ecological risk (ECCC 2018). The results are summarized in Table 6-1. Based on the outcome of the ERC-I analysis, talc is considered unlikely to be causing ecological harm.

**Table 6-1. Ecological risk classification of inorganics results for talc**

| Monitoring (total/extractable) | Monitoring (dissolved) | Modelling (s.71 of CEPA) | Modelling (NPRI) | Modelling (CBSA) | Overall ERC-I score |
|---|---|---|---|---|---|
| NA | NA | Low | NA | Low | Low |

Abbreviations: NA, not available.

# 7. Potential to cause harm to human health

## 7.1 Health effects assessment

Talc was previously reviewed internationally by the IARC, and an IARC monograph is available (IARC 2010). Additionally, talc was reviewed by the U.S. EPA, JECFA, and Danish EPA (U.S. EPA 1992; JECFA 2006; Danish EPA 2016). Talc was also assessed by the MAK-Commission in Germany and by the CIR Expert Panel (MAK-Commission 2012, CIR 2013; Fiume et al. 2015).

As part of a weight of evidence assessment (Health Canada [modified 2017]), a literature search was conducted from January 2015 (the year prior to the most recent assessment (the 2016 Danish EPA review)) to September 2020, to identify additional studies of adequate quality and relevance for inclusion in the screening assessment. No additional health effects studies that could impact the risk characterization (i.e., result in different critical endpoints or lower points of departure than those stated in existing reviews and assessments) for oral, dermal, or inhalation exposures were identified. For perineal exposures, recently published literature was identified and considered in the assessment.

The health effects of talc are outlined by route of exposure in the following sections.

### Toxicokinetics

Talc is poorly absorbed via the oral route of exposure. Following gavage administration of radiolabelled talc to rodents, the majority of the administered dose (AD) remained in the gastrointestinal (GI) tract and was eliminated in the feces (≥ 95.8% of AD) within 3 to 4 days of dosing (Wehner et al. 1977a; Phillips et al. 1978). Less than 2% of the AD was recovered in the urine; however, this was mainly attributed to contamination from feces during collection, with true absorption and urinary clearance expected to be even lower. At 24 hours post administration, less than 2% of the AD remained in the carcass of hamsters; no radioactivity was detected in mouse carcasses at this time point. In rats and guinea pigs, only trace amounts of radioactivity remained in the GI tract at 10 days post administration.

As an insoluble solid, talc is not expected to be absorbed when applied to healthy and intact skin. There are no indications of dermal absorption following talc exposure (MAK-

Commission 2012). According to a review by the MAK-Commission (2012), there are no indications of metabolism via typical degradation pathways, independent of route of exposure, from which toxicologically relevant degradation products may develop.

In general, inhaled particles 5 to 10 µm are eliminated from the respiratory tract via mucociliary clearance, while smaller particles (< 5 µm) can be transported to the smaller airways and deposit deep in the alveolar region of the lung, relying on alveolar macrophage mediated clearance (Leikauf 2013). The shape and surface area will also influence lung deposition and clearance (Steiling 2018). In female Syrian hamsters that were administered aerosolized neutron-activated cosmetic talc by nose-only inhalation at concentrations of 40 to 75 mg/m$^3$ (95% pure; median mass aerodynamic diameter (MMAD) 6.4 to 6.9 µm) over a 2-hour exposure period, 6% to 8% of the AD was deposited into the alveoli (Wehner et al. 1977b). The biological half-life following a single exposure was estimated to be between 7 and 10 days, with complete alveolar clearance after 4 months. There was no translocation of talc from the respiratory tract to the liver, kidneys, ovaries, or other parts of the body. Lung clearance was noted to be longer in other species. The Danish EPA (2016) remarked that talc, including the respirable fraction, is not absorbed following inhalation, but is retained in the lung tissue. They further stated that lung burden correlates to exposure concentrations, with clearance of talc from the lung impaired to a greater extent with increasing exposure concentrations. Pulmonary retention half-lives for talc particles in the lungs of rodents from the U. S. National Toxicology Program (NTP) chronic inhalation studies were estimated to be as long as 300 days in rats and 1000 days in mice (revisit of NTP data by Oberdorster 1995). Other authors (Pickrell 1989; MAK-Commission 2012) noted similar findings indicating that with repeat exposures, alveolar clearance in rats may be impaired at concentrations of only 2 mg talc/m$^3$ air.

Limited information is available for the toxicokinetics of talc particles following perineal exposure. The available information is summarized in the section on *Perineal exposure to talc* below, under *Mode of action*.

## Health effects

### Oral route of exposure

Talc was considered to be of low concern with respect to human health via oral exposure. Repeated-dose testing via oral exposure to talc in animals did not produce any adverse effects with respect to repeated-dose toxicity, carcinogenicity, reproductive/developmental toxicity, or mutagenicity (Gibel et al. 1976; Wagner et al. 1977; NTP 1993; IARC 2010; Danish EPA 2016).

Talc has not been shown to produce adverse effects when ingested orally. As a result, the use of talc in various tablet formulations was not considered hazardous via the ingestion route (Hollinger 1990; U.S. EPA 1992).

In addition, the Commission of the European Communities' report on Dietary Food Additive Intake in the European Union identified talc as having an acceptable daily intake (ADI) of "not-specified." The JECFA has also assessed talc and assigned an ADI of "not specified" due to the lack of toxicity from oral exposure. The substance was considered not to be a hazard to human health at oral intake levels noted in total diet surveys, which represents the main sources of oral exposure for this substance (IARC 1987; EU [modified 2001]). Furthermore, talc is considered "generally recognized as safe" for specific uses in food packaging in the United States (U.S. FDA GRAS list) without being subject to pre-market approval requirements (U.S. FDA 2019a, b).

**Dermal route of exposure**

There are limited data available on repeated-dose studies via dermal exposures to talc (Danish EPA 2016). In the available literature, only one repeated-dose dermal toxicity study was identified (Wadaan 2009). Severe limitations were noted for this study, including a lack of information on the test substance and the dose applied, as well as a lack of detail regarding the test animals. Skin dryness and erosion were noted; however, application sites were shaved, indicating that talc may have been applied to broken skin. Additionally, there were no indications of irritation, sensitization, or dermal absorption following exposure to unabraded and/or non-diseased skin (MAK-Commission 2012). A 3-day occlusive application of pharmaceutical-grade talc did not show any signs of irritation in five human volunteers (Frosch and Kligman 1976, as reported in MAK-Commission 2012).

Case reports, however, do indicate that the application of talc to diseased or broken skin can cause the formation of granulomas, particularly if the talc particles have a large diameter (MAK-Commission 2012; CIR 2013; Fiume et al. 2015). In addition, granulomas have been observed in the umbilical regions of infants, in the testes, on the vocal cords, in the urinary tract, and during phlebectomies following contact with talc-powdered surgical gloves (Ramelet 1991, as reported in MAK-Commission 2012; Simsek et al. 1992, as reported in MAK-Commission 2012). As a result, the CIR concluded that "talc should not be used on skin where the epidermal barrier is removed or on skin that has greater than first degree burns."

Although dermal contact with talc is expected from the use of various products available to consumers, talc is a chemically inert, solid powder that is insoluble in water (Table 3-1). As a result, it does not penetrate intact skin, and therefore systemic absorption through the skin is not expected. Consistent with other international regulatory and advisory bodies (Danish EPA, U.S. EPA, MAK-Commission, U.S. FDA, and JECFA), a dermal health effects endpoint has not been identified for talc.

**Inhalation route of exposure**

*Human studies*

Epidemiological data for workers exposed to talc via inhalation have been reviewed and discussed by the U.S. EPA (1992), IARC (2010), MAK-Commission (2012) and Danish EPA (2016).

The Danish EPA (2016) noted that talc is not absorbed via inhalation. Rather, particles are retained in the lung, and lung burden is reported to increase proportionally with exposure concentration and frequency. The Danish EPA (2016) detailed epidemiological data that noted mortalities in workers due to lung diseases following exposures to talc. However, it was stated that there was no increase in the lung cancer rate in talc millers in the absence of exposure to carcinogens. A recent meta-analysis by Chang et al. (2017) reported a positive association with lung cancer in workers exposed to talc. However, co-exposure to other hazardous materials in the workplace and smoking were not adequately accounted for.

The chronic inhalation of talc leads to lung function disorders and fibrotic changes in humans. Since talc particles are persistent, they have the potential to accumulate in human lung tissue, which may lead to both an impairment of the self-cleaning mechanism of the lungs (reduced ability to fight infections) and inflammatory changes and fibrosis. Talc particles may be enclosed in a foreign-body granuloma as the result of an inflammatory reaction. The mobility of the macrophages is restricted by phagocytized talc particles, leading to changes in the function of these cells and subsequently to chronic inflammatory reactions (Gibbs et al. 1992).

In humans, there are reports of pure talc-induced pneumoconiosis or talcosis following repeated inhalation exposure to talc. Talcosis has been reported to occur in miners, millers, rubber workers, and other occupational groups exposed to talc without asbestos or silica (Fine 1976; Vallyathan and Craighead 1981; Feigin 1986; Gibbs et al. 1992; Wild et al. 1995; Akira et al. 2007) after long term exposures at air concentrations estimated to be as low as < 1 mg/m$^3$. The Danish EPA relied upon a more recent longitudinal survey of French and Austrian talc workers (Wild et al. 2008) in which the prevalence of small radiological opacities and decreases in lung function parameters were related to cumulative exposure at study inclusion. Previous samples taken from the French cohort (Wild et al. 1995) indicated a correlation between talc exposures and lung effects. However, as the follow-up study progressed, talc exposure did not produce additional changes. It should be noted that confidence intervals for exposures within the study were large, indicating high variability in the data. The mean estimated talc dust concentration during the mean duration of follow-up (14.5 years) was 1.46 mg/m$^3$ (Wild et al. 2008).

With respect to non-occupational human exposures, cases have been reported of individuals exposed to talc (from acute to prolonged exposures) who seek treatment for non-specific complaints, including progressive exertional dyspnea and dry or productive cough, with indications of lung lesions (Marchiori et al. 2010; Frank and Jorge 2011). Talcosis has been shown to occur in children and adults, with symptoms that developed shortly after acute to short-term exposure or up to 10 years later (Patarino et al. 2010;

Shakoor et al. 2011). Inhalation of talc has been known to cause pulmonary effects, even following single acute exposures, as reported in a 10-year-old child who had a history of a single exposure to talc at two years of age (Cruthirds et al. 1977). Another case report detailed a 7-year-old child who developed asthma and reduced lung function after a single exposure event (Gould and Barnardo 1972). Additionally, a 52-year-old woman who used baby talcum powder regularly, at least twice a day (usually after bathing for personal hygiene and habitually applying it to her bed sheets nightly) for 20 years, was reported to have dyspnea, along with a persistent dry cough and unintentional rapid weight loss. A radiographic exam noted evidence of interstitial lung disease with fibrosis (Frank and Jorge 2011).

Other relevant case reports include that of a 55-year-old woman, occupationally exposed to talc as a dusting agent on packed rubber balls from 1958 to 1968, who was reported to develop dyspnea during the first 5 years after exposure (Tukiainen et al. 1984), and a 62-year-old woman occupationally exposed to talc for 5 years who was reported to have progressive lung fibrosis for more than 40 years (Gysbrechts et al. 1998).

*Animal studies*

Similar to what has been observed in humans, inhalation of talc in animals may elicit inflammation and lead to lung disease (Sato et al. 2020). Inhalation studies conducted with talc in animals have been cited and reviewed by the U.S. EPA (1992), IARC (2010), MAK-Commission (2012) and Danish EPA (2016) and are summarized in this section. A literature search was conducted from the year prior to the most recent assessment to September 2020, and no studies were identified that produced lower points of departure or different critical endpoints than the studies summarized in this section. In addition, a number of studies were noted to have significant limitations and are not considered further in this assessment.

In a repeated-exposure study conducted by the U.S. NTP, groups of F334/N rats were exposed to aerosolized talc (MMAD 2.7 to 3.2 µm; Geometric Standard Deviation (GSD) 1.9) via the inhalation route of exposure. Test animals were exposed (whole-body) for 6 hours per day, 5 days per week, for up to 113 weeks (males) or up to 122 weeks (females) to aerosols of 0, 6, or 18 mg/m$^3$ talc (49 or 50 males per group, 50 females per group) (NTP 1993). Mean body weights of rats exposed to 18 mg/m$^3$ talc were slightly lower than those of controls after week 65. No clinical observations were attributed to talc exposure. Absolute and relative lung weights of male and female rats exposed to 18 mg/m$^3$ talc were significantly greater than those of controls. Inhalation exposure produced a spectrum of inflammatory, reparative, and proliferative processes in the lungs. Granulomatous inflammation, which was evident as early as 6 months (first histopathological examination), occurred in nearly all exposed rats, and the severity increased with exposure duration and concentration. Hyperplasia of the alveolar epithelium and interstitial fibrosis occurred in or near the foci of inflammation in many exposed rats, while squamous metaplasia of the alveolar epithelium and squamous

cysts were also occasionally seen. Accumulations of macrophages (histiocytes), most containing talc particles, were found in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In exposed male and female rats, there was a concentration-related impairment of respiratory function, beginning at 11 months, which increased in severity with increasing exposure duration. The impairment was characterized by reductions in lung volume (total lung capacity, vital capacity, and forced vital capacity), lung compliance, gas exchange efficiency (carbon monoxide diffusing capacity), and non-uniform intrapulmonary gas distribution (NTP 1993). Based on these results, a lowest observed adverse effect concentration (LOAEC) of 6 mg/m$^3$ was established for non-cancer lung effects.

In female rats, at 18 mg/m$^3$ talc, the incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined) were significantly greater than those of controls (NTP 1993). The incidences of lung neoplasms in exposed male rats were similar to those in controls. Adrenal medulla pheochromocytomas (benign, malignant, or complex [combined]) occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m$^3$ talc groups were significantly greater than those of controls (NTP 1993).

The NTP (1993) concluded that there was some evidence of carcinogenic activity of talc in male rats on the basis of an increased incidence of benign or malignant pheochromocytomas of the adrenal gland. They also concluded that there was clear evidence of carcinogenic activity of talc in female rats on the basis of increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.

In a subsequent symposium, experts from the NTP, along with academic, industry, and government experts, re-examined the results of the chronic inhalation studies. The general consensus from the expert panel was that the highest dose tested (18 mg/m$^3$) exceeded the maximum tolerated dose (MTD) and, for that reason, the neoplasms noted were considered not relevant to human health risk assessment (Carr 1995). A similar conclusion was reported by Warheit et al. (2016). The Danish EPA (2016) and the MAK-Commission attributed lung tumours in female rats to the general particle effect of granular biopersistent dusts, which manifests as lung tumours in rodents only, an effect that would not be specific to the talc particles. They also attributed the pheochromocytomas to an increase in cell proliferation due to hypoxia, which was considered to be a high-dose effect (MAK-Commission 2012).

In another chronic NTP study, B6C3F1 mice were exposed to aerosolized talc via the inhalation route (NTP 1993). Test animals (47 to 49 males per group, 48 to 50 females per group) were exposed (whole-body) for 6 hours per day, 5 days per week, for up to 104 weeks to aerosols of 0, 6, or 18 mg/m$^3$ talc (MMAD 3.3 to 3.6 µm; GSD 1.9 to 2.0). Survival and final mean body weights of male and female mice exposed to talc were similar to those of controls. Animals appeared normal in cage-side observations conducted throughout the study. Chronic active inflammation and the accumulation of

macrophages, which contained talc, were observed in the lungs of mice exposed to both concentrations of talc. In contrast to rats, hyperplasia of the alveolar epithelium, squamous metaplasia, or interstitial fibrosis were not associated with the inflammatory response in mice, and the incidences of lung neoplasms in exposed and control groups of mice were similar. Accumulations of macrophages (histiocytes) containing talc particles were also present in the bronchial lymph node. The critical effect level and corresponding health effects endpoint was a LOAEC of 6 mg/m$^3$ for non-cancer lung effects (NTP 1993).

Doses used in its chronic studies were selected by the NTP on the basis of the results of a 4-week inhalation study (1993) in which rats and mice were exposed to talc at 0, 2, 6, or 18 mg/m$^3$ for 6 hours a day, 5 days a week. Lung burden was noted to be increased in a dose-dependent manner, with overload noted by the study authors at 6 and 18 mg/m$^3$ in rats but not at any dose in mice.

In a review of the NTP studies, Oberdorster (1995) revisited the lung deposition data and particle accumulation kinetics in the lungs of rats and mice, demonstrating that impaired clearance and lung overload was reached at 6 mg/m$^3$ and above, for both sexes, in rats and mice. A recent review by Bevan et al. (2018) explores the issue of lung overload and lung cancer associated with toxicity testing of poorly soluble particles in rodents. They concluded that while the evidence suggests that the rat lung model is unreliable as a predictor for human lung cancer risk associated with these substances, it is a sensitive model for detecting various threshold inflammatory markers, with utility for use in non-neoplastic risk assessment.

A no observed adverse effect concentration (NOAEC) of 2 mg/m$^3$ was derived from the NTP 4-week study, on the basis of increased lung burden and impaired clearance at a LOAEC of 6 mg/m$^3$ following 4 weeks of dosing. At the same concentration (6 mg/m$^3$), granulomatous inflammation and alveolar epithelial hyperplasia were noted at a 6-month interim sacrifice in the chronic rat inhalation study, and interstitial fibrosis and impaired lung function were noted in some animals at 11 months. As noted previously, following a single exposure in rats, the biological half-life for ciliary clearance was between 7 and 10 days, indicating that previous exposure would not have cleared prior to subsequent exposures, leading to a build-up in lung tissue. In a re-examination of the NTP lung burden data, Oberdorster (1995) estimated that lung retention half-lives of talc particles were between 250 and 300 days in the rat chronic study.

The Danish EPA (2016) established a health-based quality criterion for ambient air ($QC_{air}$)[10] of 0.004 mg/m$^3$, based on both animal and human data. The LOAEC of 6 mg/m$^3$ from the chronic NTP studies (mice and rats) and the NOAEC of 1.5 mg/m$^3$ for

[10] The health-based quality criterion in ambient air ($QC_{air}$) is a reference concentration that refers to the maximum permissible contribution to air from industrial sources.

talc-induced non-cancer lung effects in the longitudinal survey of French and Austrian talc workers (Wild et al. 2008) were each considered as relevant points of departure by the Danish EPA. After incorporating uncertainty factors (250 for the animal endpoint and 100 for the human endpoint) to address inherent uncertainties within the database (e.g., limitations in the human and animal data, variability within the human population), a $QC_{air}$ of 0.004 mg/m$^3$ was established by the Danish EPA.

Although human occupational studies and case studies are available, these studies do not provide accurate measures of exposure for use in establishing points of departure for quantitative risk characterization. However, human studies do note a similar range of lung effects and disease as animal models. Results from the above-noted animal studies were therefore selected for the non-cancer risk characterization. On the basis of the NTP studies with rats and mice exposed to cosmetic-grade talc, a NOAEC of 2 mg/m$^3$ for non-cancer lung effects is considered to be appropriate for the inhalation route of exposure for short- or long-term use. Given the long half-life and slow lung clearance of talc from the lungs, even episodic exposures would be expected to increase lung load. The NOAEC of 2 mg/m$^3$ was derived from a study in which animals were exposed on an intermittent basis (6 hours per day, 5 days a week). It was adjusted to a concentration that represents continuous exposure, using the U.S. EPA guidance on inhalation risk assessment[11] (U.S. EPA 1994, 2009). The adjusted NOAEC for non-cancer effects is 0.36 mg/m$^3$. This adjustment is considered appropriate to apply when the available data indicate that both concentration and time (c x t), not concentration alone, are likely to affect the toxicity observed.

**Perineal exposure to talc**

In 2006, the IARC classified perineal use of talc-based body powder as “possibly carcinogenic to humans” (Group 2B) on the basis of limited evidence in humans. The IARC reported that “many case-control studies of ovarian cancer found a modest, but unusually consistent, excess in risk, although the impact of bias and potential confounding could not be ruled out” (IARC 2010).

In 2014, in response to citizen petitions, the U.S. FDA reviewed the available scientific information and did not find that the data presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer. However, the U.S. FDA recognized that a possible association may exist. In their correspondence to

[11] This adjustment was made according to guidance and equations outlined in the U.S. EPA Supplemental Guidance for Inhalation Risk Assessment (U.S. EPA 2009) and the U.S. EPA Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA 1994). Adjustment of duration to a continuous exposure scenario is done through the use of Equation 1 from U.S. EPA 2009, i.e., NOAEC[ADJ] = E × D × W, where the NOAEC[ADJ] (mg/m$^3$) = the no-observed adverse effect level (NOAEC) adjusted for the duration of the experimental regimen; E (mg/m$^3$) = the NOAEC or analogous exposure level observed in the experimental study; D (h/h) = the number of hours exposed/24 hours; and W (days/days) = the number of days of exposure/7 days. The NOAEC[ADJ] = 2 mg/m$^3$ × 6h/24h × 5d/7d = 0.36 mg/m$^3$.

the petitioner they note; “while the growing body of evidence to support a possible association between genital talc exposure and serous ovarian cancer is difficult to dismiss, the evidence is insufficient for FDA to require as definitive a warning as [you] are seeking” (U.S. FDA 2014).

The National Cancer Institute’s Physician Data Query for Health Care Professionals (NCI 2019) states that “[t]he weight of evidence does not support an association between perineal talc exposure and an increased risk of ovarian cancer.”

The CIR Expert Panel (2013) determined that there is no causative relationship between cosmetic use of talc in the perineal area and ovarian cancer and that talc is safe in the practices of use and concentration described in the CIR safety assessment. Issues noted by the CIR included a lack of consistent statistically significant positive associations across all studies; small risk ratio estimates; a failure to rule out other plausible explanations such as bias, confounders, and exposure misclassifications; and a lack of evidence from studies of occupational exposures and animal bioassays (CIR 2013; Fiume et al. 2015).

Several publications became available after the IARC, U.S. FDA and CIR assessments and suggest that the relationship between perineal talc exposure and ovarian cancer is causal (Narod 2016; Penninkilampi and Eslick 2018; McTiernan 2019; Taher et al. 2019). Other authors do not indicate a causal relationship (Huncharek and Muscat 2011; Berge et al. 2018; Goodman et al. 2020; Johnson & Johnson Consumer, Inc. 2020).

The etiology of most ovarian tumours has not been well established, and ovarian cancer is a relatively rare disease (NASEM 2016; AICR 2020; CTFPHC 2020; NCI-SEER 2020). There are a number of different tumour types with characteristic histologic features, distinctive molecular signatures, and disease trajectories. Moreover, these tumours are heterogeneous and can arise from different tissues of the female reproductive tract, including the fallopian tube epithelium (Piek et al. 2001; Piek et al. 2003; Finch et al. 2006; Kindelberger et al. 2007; Przybycin et al. 2010; Morrison et al. 2015; NASEM 2016). Ovarian tumours can be grouped into categories (e.g., epithelial ovarian cancer, germ cell tumours, gonadal stromal tumours, metastatic neoplasms). Epithelial ovarian cancers are often designated as Type I or Type II, with further subdivision within each type. Type I tumours have characteristics quite distinct from Type II tumours, and research supports that they have different molecular pathways and may not be ovarian in origin (Kurman and Shih 2011; Seidman et al. 2011; Kuhn et al. 2012; Kurman and Shih 2016).

Tumour subtypes are one of the many subgroup analyses conducted in several of the epidemiology studies and reviews. However, there was very little consistency in whether, or how, these subgroup analyses were conducted across the available studies, thereby leaving the analyses limited and likely underpowered (low sample sizes). Furthermore, there is considerable uncertainty for how subgroup data should be

examined, in particular, for the tumour subtypes. Therefore, subgroup analyses will not be further examined in this assessment.

*Mode of action*

The possibility that talc could migrate to the ovaries from perineal use was postulated following work by Henderson et al. (1971). In terms of disposition, talc particles were identified in 10 of 13 human ovarian tumours and 12 of 21 cervical tumours but were also found in 5 of 12 “normal” ovarian tissues removed from patients with breast cancer (Henderson et al. 1971). A follow-up study was conducted in order to control for talc contamination (e.g., from surgeons’ gloves) and again talc was found in all samples: three normal ovaries, three cystic ovaries and three adenocarcinomas (Henderson et al. 1979). There was no information provided on the patients in these studies with respect to history of perineal talc use.

In a separate study, ovaries from 24 patients undergoing incidental oophorectomy were examined; 12 women reported frequent perineal talc use (ever-users) and the other 12 women were non-users. Talc particles were detected in all 24 cases (both ever- and non-users) and there was no relation found between reported levels of exposure and talc particle counts in ovaries (Heller et al. 1996). Wehner (2002) attributed the talc in the non-users to (a) possible sample contamination, because some studies using negative controls resulted in particle counts similar to the test sample; and/or (b) possible false positives due to the use of a single radioactive tracer. Heller et al. (1996) hypothesized that talc use during diapering could also contribute to the ovarian particle burden.

A case report has been described of a woman with advanced ovarian serous carcinoma known to have used talc in her genital area daily for 30 years. Talc was shown to be present in macrophages within pelvic lymph node tissue. It was therefore unlikely to be due to surface contamination and likely was caused by talc migration up the reproductive tract to the ovaries (Cramer et al. 2007; Campion et al. 2018). In a more recent study, McDonald et al. (2019b) aimed to differentiate the presence of talc in pelvic lymph nodes due to talc exposure versus contamination. The study showed that the methods used for assessment and quantification of talc can drastically affect the findings. Digestion of the tissue sample may be more greatly influenced by contamination than using *in situ* scanning electron microscopy/energy dispersive X-ray analysis (*in situ* SEM/EDX). In one experiment, nodes in 22 patients with various types of ovarian tumours were examined (45% had used talc in their genital areas and 73% had used it as a body powder) by digestion and regular SEM/EDX. A measure of surface contamination (presence of material along specimen edge) was also estimated for each sample. Overall, genital talc users had higher talc counts than non-users, but the association was of borderline significance. However, after adjusting for surface contamination, talc burden in nodes correlated strongly with genital talc use. In a second experiment, 19 lymph node specimens from 10 carcinoma cases (talc exposure unknown) were assessed by *in situ* SEM/EDX without digestion, which allowed for

distinction of interior tissue versus exterior surfaces. This portion of the study confirmed talc as surface contamination particles (McDonald et al. 2019b).

Migration or retrograde movement of talc particles from the vagina to the ovaries has been identified as a plausible explanation of the above findings (i.e., talc particles in the upper reproductive tract) (Henderson et al. 1986; Heller et al. 1996; Cramer et al. 2007). The U.S. FDA (2014) stated "[w]hile there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable." Schildkraut et al. (2016) suggested that talc particles might also translocate to the ovaries following inhalation exposure to fine talc particles. However, these findings were not evident in the hamster inhalation study summarized above under *Toxicokinetics* (Wehner et al. 1977b). Some authors have noted the idea that the uterus and fallopian tubes act as a peristaltic pump to help retrograde movement of sperm (Zervomanolakis et al. 2007), which could also help transfer particles up the reproductive tract. Studies specifically assessing potential movement of talc particles through the human body were not identified in the literature. The limited information that was available reported mixed results; however, the possibility of translocation of fine and ultrafine particulate matter, in general, has been noted (Peters et al. 2006).

A suspension of talc (100 mg/ml in saline) was introduced into the cervical canal of female rats (n = 8). Half of the rats were sacrificed 5 days later and the remaining rats went on to receive up to four further instillations. A similar procedure was conducted on an additional 12 rats; however, the suspension was deposited into the vagina and animals were sacrificed after 24 hours, 48 hours or 4 days. Talc particles were detected in the ovaries of all the rats that received intrauterine instillations as well as the rats that received intravaginal treatment killed after 4 days. There was no talc detected in the control rats, nor in the rats receiving intravaginal treatment that were killed at 24 hours or 48 hours (Henderson et al. 1986). Conversely, in other species, no translocation of talc into the ovaries was detected after single or multiple intravaginal applications. Female rabbits were given a single dose (n = 3) or six daily doses (n = 3) of a radiolabelled talc suspension intravaginally and killed 3 days following the last dose. Radioactivity was detected at the site of administration in all rabbits, and a small amount was found in the cervix and fallopian/uterine tubes in the repeated dose rabbits; however, no radioactivity was detected in the ovaries (Phillips et al. 1978). Similarly, in monkeys receiving 30 applications daily over consecutive work days of neutron-activated talc in saline deposited in the posterior vaginal fornix, samples from the vagina and cervix contained talc, whereas samples from the uterus or ovaries did not (Wehner et al. 1986). This confirmed results from the pilot study in an earlier paper with fewer monkeys and only a single dose, in which no measurable talc was found deposited in the uterine cavity or further up the reproductive tract (Wehner et al. 1985).

Translocation of other inert particles, similar in size to talc, has also been studied in humans and animals. Retrograde migration was studied in rabbits administered a lubricant powder intravaginally. There were no overall statistically significant differences

between the control and experimental animals; however, some measured parameters (large particles from peritoneal fluid cell pellets and small particles in cervix) did show significant differences and indicated that the possibility of retrograde migration could not be excluded (Edelstam et al. 1997). A subsequent study in humans was conducted where patients (n = 12 to 17) undergoing elective hysterectomy were examined either with powdered gloves or powder-free gloves at 1- or 4-days pre-operatively. For those examined 1-day pre-operatively, statistically significant increases in large and small starch particles were found in the cervix, uterus and tubes. At 4-days pre-operatively, increases were only significant in the cervix and uterus. Particles were however found in three control patients, and two of the test subjects had no particles detected (Sjosten et al. 2004).

Three human patients undergoing a scheduled hysterectomy had a suspension of carbon particles deposited in the posterior fornix of the vagina after general anesthesia was induced. Carbon particles were recovered from the fallopian tubes of two of the three women approximately 30 minutes following administration. No carbon particles were found in the fallopian tubes of the third patient 20 minutes after administration. There were no control patients in this study (Egli and Newton 1961). De Boer (1972) conducted a similar experiment using a colloidal suspension of carbon placed into patients about to undergo abdominal surgery. Carbon material was found in the fallopian tubes of more than 50% of the patients when the suspension was placed in the uterine cavity but only once in 37 observations when it was placed in the vagina. Venter and Iturralde (1979) reported a study where radiolabelled human albumin microspheres were deposited in the posterior fornices of 24 patients admitted to hospital for elective gynecological surgeries. Sixteen had radioactive tracer in the uterus, fallopian tubes and/or ovaries, five were negative and the remaining three were excluded due to technical error. Technetium-labelled albumin macrospheres were also used by Kunz et al. (1996) and Kissler et al. (2004). A suspension was placed into the posterior vaginal fornix of 64 women during the early, mid- and late follicular phases of the cycle. Ascension of the macrospheres to the tubes occurred rapidly and quantitatively increased with progression of the follicular phase (Kunz et al. 1996). Kissler et al. (2004) found that uterine contractibility was influenced by estradiol levels. The rate and direction of contractions varies throughout the cycle of nonpregnant humans. Small and frequent contractions in retrograde direction occur from the end of menstruation until the late proliferative phase; during menstruation, the direction reverses.

With respect to talc and induction of tumours, local chronic irritation leading to an inflammatory response is one possible mechanism of tumour progression that is frequently hypothesized in the literature (Muscat and Huncharek 2008; Penninkilampi and Eslick 2018; Taher et al. 2019; O'Brien et al. 2020). An inflammatory response associated with talc has been clearly demonstrated in lung tissue (Sato et al. 2020) and utilized clinically in pleurodesis (Van den Heuvel et al. 1998; Genofre et al. 2007; Arellano-Orden et al. 2013), and there is support for an association of inflammation and increased risk of ovarian cancer (Cheng et al. 2000; Yan et al. 2006; NASEM 2016; Rasmussen et al. 2017). Persistent indications of inflammation (including C-reactive

protein, tumour necrosis factor, and other inflammatory markers) are detected in the blood of women prior to a diagnosis of ovarian tumours (Trabert et al. 2014), while other inflammatory markers have been found in the blood of women who used talc products daily for more than 20 years (Williams et al. 2014). Zeng et al. (2016) performed a meta-analysis of eight epidemiology studies and determined that elevated levels of C-reactive protein was associated with a significantly increased risk of ovarian cancer. In an animal study (summarized below), Keskin et al. (2009) measured an increase in the number of inflammatory cells in all genital tissues of rats intravaginally exposed to talc for 3 months. It should be noted however that the rats also developed infections over the course of the study which could have led to the increase in inflammatory cells.

A recent study (Fletcher et al. 2019) was conducted to determine the effect of talc on the expression of enzymes and markers associated with inflammation, and the effect on cell proliferation and apoptosis in normal cells compared to epithelial ovarian cancer cells was also examined. There was a dose-dependent significant increase in key prooxidants and a decrease in key antioxidant enzymes in all talc-treated cells compared to controls. It was found that talc exposure induced specific point mutations that are known to alter the activity of some of these enzymes. There was an increase in inflammation as determined by a significant increase in the tumour marker CA-125. And lastly, talc-exposed cells had significantly induced cell proliferation and decreased apoptosis. Such changes (shifts in key redox and inflammatory markers, enhanced cell proliferation and apoptosis inhibition) are all hallmarks of ovarian cancer (Fletcher et al. 2019) and support the hypothesis that talc exposure may lead to ovarian cancer through inflammatory mechanisms.

In another recent study (McDonald et al. 2019a), five cases (patients with ovarian cancer and a history of perineal talc use) and six controls (patients with ovarian cancer and no genital exposure to talc) were assessed. Surgically resected pelvic tissues (ovary, fallopian tube, cervix/uterus, lymph node) were examined by polarized light microscopy (PLM), SEM and EDX. Talc was found in at least two and up to four pelvic organ sites distant from the perineum in all five of the cases, yielding an aggregate total of 503 talc particles for the five cases. This can be compared to the four total talc particles found in the controls (two in the ovary of one patient and two in the fallopian tube of another patient). The presence of asbestos fibres was also investigated and nothing above the level of detection was measured in any of the subjects (cases or controls). Findings also showed accumulation of talc in the cytoplasm of tissue macrophages in several of the tissue sites of the five cases, which may substantiate the inflammatory potential of talc. Finally, this study supports the hypothesis of the migration of talc from the perineal region through lymphatic pathways by demonstrating the presence of talc in multiple pelvic tissues and lymph nodes simultaneously (McDonald et al. 2019a). Some further work was done (Johnson et al. 2020) to compare talc particles from commercially available powders to those found in pelvic tissues taken from 11 randomly selected ovarian cancer patients with a known history of long-term perineal talc use. PLM and SEM/EDX were employed to measure the talc particles, and extensive measures were taken to control for contamination. The talc particles taken

from tissues of the patients were most often located within benign tissue, reactive fibroblastic tissue, or chronically inflamed tissue near a tumour, rather than within tumours; the presumption is that talc accumulates in benign tissue some time prior to the tumour developing. The particle size and dimensions of talc particles found in the commercial samples are consistent with those found in the pelvic tissues of the patients: 77.7% of commercial samples and 83.5% of talc from tissues fall within the same ranges for aspect ration and area. This lends support to the idea that externally-applied talc can migrate from the perineal area (Johnson et al. 2020).

The effect of talc particles in the presence of estrogen was investigated in culture with murine ovarian surface epithelial cells. Co-stimulation of macrophages with estradiol and talc produced an additive effect on reactive oxygen species production and permitted a higher number of cancer cells to survive. Talc alone, and especially in combination with estradiol, produced changes in gene expression that could have promoted a pro-tumorigenic environment and less efficient tumoricidal activity of the macrophages. Control particles (titanium dioxide, urban air particulates or diesel exhaust particles) did not produce the same effects (Mandarino et al. 2020). These results align with the earlier findings of Buz'Zard and Lau (2007) that talc increased cell proliferation and reactive oxygen species generation and induced neoplastic transformation in ovarian cells and polymorphonuclear neutrophils *in vitro*, suggesting that it may contribute to ovarian neoplastic transformation. Similarly, talc was noted to induce a greater inflammatory response than other poorly soluble particles in a recent study in hamsters (Sato et al. 2020). Collectively, these results suggest that talc is different from other poorly soluble particles and demonstrates a tumour-promoting activity.

Another possible mode of action put forth in the scientific literature is immune mediated. It has been suggested that talc particles need not reach the ovaries but only need to reach the lower genital tract, where they could trigger changes (such as the production of heat shock proteins and/or decreased levels of antibodies) that could contribute to ovarian cancer (Cramer et al. 2005; Muscat et al. 2005). Human mucin 1 (MUC1) is expressed in high levels by ovarian cancer (Gendler and Spicer 1995; Deng et al. 2013). Mucins are proteins involved in the formation of mucous barriers on epithelial surfaces (Gendler and Spicer 1995). Anti-MUC1 antibodies may have a protective effect; patients generate immunity against MUC1 produced by their tumours (Cramer et al. 2005). The Cramer et al. (2005) study used an enzyme-linked immunosorbent assay to measure anti-MUC1 antibodies in women. It was found that the use of talc in the perineal area was associated with significantly decreased levels of antibodies to MUC1. Cramer (2012) further hypothesized that chronic talc use can affect the tissues that express MUC1, leading to an immune-tolerance and lower anti-MUC1 antibodies, thus increasing the risk for ovarian cancer. Pinheiro et al. (2010) also studied anti-MUC1 levels and ovarian cancer in a large cohort. Although the results were not stratified with respect to talc use specifically, the authors found that anti-MUC1 antibodies, when evaluated several years prior to diagnosis, may be associated with decreased risk of ovarian cancer in subjects less than 64 years of age at assessment.

*Animal studies*

While some animal studies have investigated the effect of talc on the ovaries, rodents are poor experimental models for perineal studies for a number of reasons. Ovulation, including the number of oocytes generated and the length of cycle, is markedly different in rodents compared to humans (Chaffin and VandeVoort 2013). In general, epithelial ovarian tumours are rare in rodents, possibly due to the bursa surrounding the ovaries. The ovarian bursa is lacking in humans, but is necessary for normal ovulation and reproduction in rodents. This membranous pouch may offer some protection of the surface epithelium from local carcinogens (Nishida et al. 1998; Li et al. 2007). Ovarian tumours can occur in some strains of mice and rats; however, the low incidence and the length of time required for the appearance of tumours are limitations of experimental studies testing ovarian carcinogenesis (Vanderhyden et al. 2003). On account of the limitations detailed above, in addition to the challenges posed by exposing animals via the perineal route, animal data are very limited; one single-dose study (Hamilton et al. 1984) and one short-term repeated-dose study were available (Keskin et al. 2009).

A single injection of talc (in saline; 100 µl) into the bursa around the ovaries of 10 rats resulted in a cystic appearance due to distension of the bursal sac. Foreign-body granulomas without surrounding inflammation were documented in five ovaries and papillary changes were seen in the surface epithelium in four ovaries. The presence of talc was confirmed; however, the study authors hypothesized that the results could also be due to long-term exposure to steroidal hormones present in the entrapped follicular fluid within the distended bursa (Hamilton et al. 1984).

Daily perineal or intravaginal application of talc (100 mg in 0.5 ml in saline; aerosol form) to rats (n = 7) for 3 months produced evidence of foreign-body reaction, findings of infection and an increase in the number of inflammatory cells in all genital tissues (vulva, vagina, uterus, fallopian tubes, and ovaries). Two control rats also had infections. There were no cancer or pre-cancer effects observed; however, the authors noted that the study duration may have been too short to note these types of effects (Keskin et al. 2009).

No chronic or carcinogenicity animal studies by the perineal route of exposure were identified in the literature for talc.

*Human studies*

Several meta-analyses of available epidemiological data, including both case-control and cohort designs, have been published. These studies have consistently reported a positive association with ovarian cancer and perineal talc exposure, with odds ratios (OR)s ranging from 1.22 to 1.35 (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2019). Generally, the various meta-analyses were conducted with the same available

epidemiological studies. However, different studies were included or excluded for various reasons. There were also variations in defining criteria for inclusion of participants in the study, resulting in differences in the ORs for the individual studies considered. Despite this, the meta-analyses produced similar overall ORs with statistical significance. Table 7-1 shows a comparison of the three most recently published meta-analyses, namely those of Berge et al. (2018), Penninkilampi and Eslick (2018) and Taher et al. (2019).

Collectively, across the three most recent meta-analyses, there were 30 case-control studies and four cohort design studies. A high percentage of the case-control studies, 89% for Berge et al. (2018), 92% for Penninkilampi and Eslick (2018) and 85% for Taher et al. (2019), had calculated ORs greater than 1 (indicating a positive association). Approximately half of these were statistically significant. Three of the four cohort studies also reported ORs greater than 1. However, none were found to be statistically significant (Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2019). Some considerations pertaining to the cohort and case-control design studies from the meta-analyses are noted below.

Cohort studies

There are 4 cohort studies used in the meta-analyses and reported in Table 7-1. Gertig et al. (2000) and Gates et al. (2010) reported on the same cohort, i.e., the Nurses' Health Study (NHS). The NHS began in 1976 and targeted married registered nurses aged 30 to 55 years living in the 11 most populous states; 71% of those targeted returned the questionnaire. The questions pertaining to perineal powder use were not added until 1982 and were only asked once (i.e., at baseline in 1982). Participants were asked if they ever commonly used talcum, baby or deodorizing powder applied to the perineal area or sanitary napkins (NHS 2020). Gates et al. (2010) followed the subjects for 24 years (1982 to 2006), but did not assess never-users in a manner similar to other epidemiological studies. Rather, they combined the never-users with those that used powders "less than once a week." Gertig et al. (2000) accounted for the never-users alone, but their study had only 14 years of follow-up. Limitations recognized by the authors of both studies include lack of detailed exposure data (e.g., age at which use began, duration of use) and potential exposure misclassification, since the question pertaining to genital powder use was not specific to talc (Gertig et al. 2000; Gates et al. 2010). Gertig et al. (2000) also highlight the relatively short follow-up period. Gates et al. (2010) note that the greater degree of exposure misclassification over 24 years of follow up is a possible explanation for the difference in association reported in Gertig et al. (2000).

Houghton et al. (2014) used the cohort generated in the Women's Health Initiative (WHI). The original WHI study began in 1993 and concluded in 2005. Since 2005, the WHI has continued through extension studies. The subjects were limited to post-menopausal women between the ages of 50 to 79 from 40 clinical centres across the United States. As in the case of the NHS, the question pertaining to genital powder use

was not specific to talc (talc, baby, deodorizing powder) and was only asked at baseline (WHI 2020). Houghton et al. (2014) reported a mean follow-up period of 12.4 years. Duration of use was accounted for, but frequency of use was not. As noted by study authors, had both duration and frequency of use been accounted for, a better measure of intensity of use could have been conducted to assess dose-response. Other limitations mentioned by the study authors included a lack of information regarding oophorectomy after baseline and the potential for non-differential misclassification of exposure (participants still needed to recall past use and duration) (Houghton et al. 2014).

In the final cohort study, Gonzalez et al. (2016) used data collected in the Sister Study. The Sister Study was started in 2003 and recruited women aged 35 to 74 years residing in the United States and Puerto Rico who had a sister diagnosed with breast cancer. Questions regarding powder use asked at baseline were specific to talc powder, but focused only on use during the ages of 10 to 13 years as well as use in the past 12 months[12] (Sister Study 2020). Results of the Gonzalez et al. (2016) study produced the lowest calculated OR (0.73). However, the follow-up period was the shortest of all the cohort studies (less than 7 years) and talc use was assessed only for the 1-year period before the study; both of these factors were recognized as limitations by the authors. As well, as breast cancer is a risk factor for ovarian cancer development, this cohort may not be representative of the general population, since subjects are more likely than the general population to develop ovarian cancer (Gonzalez et al. 2016).

A recent analysis by O'Brien et al. (2020) revisited the available cohort studies. Data from four cohort studies (NHS, WHI, SIS and NHS II) were pooled for a total sample size of over 250 000 women. Additional cases (from the previous publications above) and a median of 11.2 years of follow-up were included. O'Brien et al. (2020) is the only published analysis that included data collected from the NHS II. The NHS II was established in 1989 and focused on oral contraceptive use, thus targeting a younger population (aged 25 to 42 years). Only a single mail-out was done, resulting in a 24% response rate. The questions regarding perineal powder use ("at least weekly") were not added until 2013 (NHS 2020), which means that fewer than 4 years of follow-up was available for the O'Brien et al. (2020) analysis. The overall OR reported by O'Brien et al. (2020) was 1.08 [0.99-1.17], and the authors concluded that there was not a statistically significant association between perineal powder use and ovarian cancer. However, the study authors recognized that the study may have been underpowered to detect a small increase in risk. Several limitations were also recognized with respect to the exposure assessment (e.g., no data collected on use after baseline, variation on exposure

[12] The Sister Study did ask again about talc powder use, including more specific questions with respect to exposure, in 2017-2019. However, data collected from these more recent questionnaires has not yet been analyzed/published.

categories, missing duration/frequency information) as well as overall limited generalizability (O'Brien et al. 2020).

Case-control studies

There are 30 case-control design studies used in the meta-analyses and reported in Table 7-1. When the studies are pooled, they generate a substantial sample size with data from different countries/geographical areas, representing a wide variety of ethnicities. As is evident in Table 7-1, the sample sizes range considerably across the studies. There are also differences in the prevalence of powder use as well as response rates, both across the studies and, typically to a lesser degree, between the cases and controls within the same study. For example, the response rates were very high for both cases (90%) and controls (94%) in Tzonou et al. (1993), whereas they were low (40% and 57%, respectively) for Mills et al. (2004). The response rate was sometimes better among cases (e.g., Merritt et al. 2008; Cramer et al. 2016) and sometimes, but less often, better among controls (e.g., Chen et al. 1992; Cook et al. 1997). Response rates were not available for all studies. Prevalence of talc use also varied, sometimes considerably, across and/or within (cases vs controls) studies. Several studies had prevalence rates for both cases and controls of over 40% (Whittemore et al. 1988; Harlow et al. 1992; Merritt et al. 2008; Schildkraut et al. 2016), whereas some reported prevalence rates of less than 10% (Chen et al. 1992; Tzonou et al. 1993), suggesting that prevalence of use may perhaps be dependent on ethnic background.

The selection of participants was restricted within each study to certain geographical areas, and some were further restricted to certain ethnicities and/or to language spoken. The specificity of the questions asked varied; some studies included questions about talc use as part of a larger questionnaire covering several potential risk factors, while other studies were more focused on talc use with detailed exposure questions (e.g., frequency, duration, brand used). The questions were almost always administered via an in-person or telephone interview by trained administrators (versus self-administered mailed questionnaires). Finally, the selection of controls differed across the studies; the majority used population-based control groups, while others chose to match cases to hospital-based controls.

A number of common limitations were recognized by the authors of the various case-control studies:

- small sample sizes (Rosenblatt et al. 1992; Tzonou et al. 1993; Ness et al. 2000; Langseth and Kjaerheim 2004; Mills et al. 2004; Moorman et al. 2009)
- limited exposure information collected (Booth et al. 1989; Harlow and Weiss 1989; Green et al. 1997; Wong et al. 1999; Rosenblatt et al. 2011)
- reliance on self-reporting (Chang and Risch 1997; Green et al. 1997; Schildkraut et al. 2016)
- low response rates, potential differences of powder use between cases and controls or not interviewing all eligible participants (Cramer et al. 1982; Whittemore et al. 1988; Chen et al. 1992; Harlow et al. 1992; Purdie et al. 1995;

Chang and Risch 1997; Cook et al. 1997; Ness et al. 2000; Mills et al. 2004; Merritt et al. 2008; Moorman et al. 2009; Rosenblatt et al. 2011; Wu et al. 2015) and

- potential for recall bias (Hartge et al. 1983; Purdie et al. 1995; Wong et al. 1999; Mills et al. 2004; Gates et al. 2008; Rosenblatt et al. 2011; Cramer et al. 2016).

**Table 7-1. Available human epidemiological studies investigating the association between perineal use of talc and ovarian cancer (Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2019)**

| Reference<br><br>Total sample size (# cases) | OR [95% CI]<br><br>(Berge et al. 2018) | OR [95% CI]<br><br>(Penninkilampi and Eslick 2018) | OR [95% CI]<br><br>(Taher et al. 2019) |
|---|---|---|---|
| **Booth et al. 1989**[a]<br>**686 (235)** | 1.29 [0.92-1.80] | 1.30 [0.94-1.80] | Not included |
| **Chang and Risch 1997**[a]<br>**1014 (450)** | 1.35 [1.03-1.76] | 1.42 [1.08-1.86] | 1.42 [1.08-1.87] |
| **Chen et al. 1992**[a]<br>**336 (112)** | 3.90 [0.91-10.60] | 3.90 [1.43-10.60] | Not included |
| **Cook et al. 1997**[a]<br>**735 (313)** | 1.50 [1.10-2.00] | 1.50 [1.11-2.02] | 1.60 [1.10-2.33] |
| **Cramer et al. 1982**[a]<br>**430 (215)** | 1.92 [1.27-2.89] | 1.60 [1.21-2.12] | 1.92 [1.27-2.90] |
| **Cramer et al. 2016**[a]<br>**4141 (2041)** | 1.32 [1.14-1.50] | 1.42 [1.03-1.95] | 1.32 [1.15-1.51] |
| **Gates et al. 2008**[a]<br>**3187 (1385)** | Not included | Not included | 1.36 [1.14-1.62] |
| **Godard et al. 1998**[a]<br>**305 (153)** | 2.49 [0.94-6.58] | 2.49 [0.94-6.58] | 2.49 [0.94-6.60] |
| **Goodman et al. 2008**[a]<br>**602 (387)** | 0.99 [0.70-1.41] | Not included | Not included |
| **Green et al. 1997**[a]<br>**1684 (824)** | Not included | 1.30 [1.06-1.60] | 1.30 [1.10-1.54] |
| **Harlow and Weiss 1989**[a]<br>**274 (116)** | 1.10 [0.70-2.10] | 1.10 [0.58-2.10] | 1.10 [0.70-1.73] |
| **Harlow et al. 1992**[a]<br>**474 (235)** | 1.50 [1.00-2.10] | Not included | 1.50 [1.00-2.25] |
| **Hartge et al. 1983**[a]<br>**306 (135)** | 2.50 [0.70-10.00] | 2.50 [0.66-9.45] | 0.70 [0.40-1.22] |
| **Kurta et al. 2012**[a]<br>**2704 (902)** | Not included | 1.40 [1.16-1.69] | 1.40 [1.16-1.69] |
| **Langseth and Kjaerheim 2004**[a]<br>**225 (46)** | Not included | Not included | 1.15 [0.41-3.23] |

| Reference<br><br>Total sample size (# cases) | OR [95% CI]<br><br>(Berge et al. 2018) | OR [95% CI]<br><br>(Penninkilampi and Eslick 2018) | OR [95% CI]<br><br>(Taher et al. 2019) |
|---|---|---|---|
| **Lo-Ciganic et al. 2012**[a]<br>**2704 (902)** | 1.34 [1.07-1.66] | Not included | Not included |
| **Merritt et al. 2008** [a]<br>**3085 (1576)** | 1.13 [0.92-1.38] | 1.17 [1.01, 1.36] | 1.17 [1.01, 1.36] |
| **Mills et al. 2004**[a]<br>**1354 (249)** | 1.37 [1.02-1.85] | 1.37 [1.02-1.85] | 1.37 [1.02-1.84] |
| **Moorman et al. 2009**[a]<br>**2143 (1086)** | 1.37 [1.05-1.80] | Not included | 1.06 [0.85-1.32] |
| **Ness et al. 2000**[a]<br>**2134 (767)** | 1.50 [1.10-2.00] | 1.50 [1.10-2.02] | 1.50 [1.10-2.05] |
| **Purdie et al. 1995**[a]<br>**1684 (824)** | 1.27 [1.04-1.54] | 1.27 [1.04-1.54] | Not included |
| **Rosenblatt et al. 1992**[a]<br>**123 (77)** | 1.70 [0.70-3.90] | 1.70 [0.72-4.01] | 1.00 [0.20-5.00] |
| **Rosenblatt et al. 2011**[a]<br>**2125 (812)** | 1.13 [0.93-1.36] | 1.27 [0.97-1.66] | 1.27 [0.97-1.66] |
| **Schildkraut et al. 2016**[a]<br>**1329 (584)** | 1.44 [1.11-1.86] | 1.44 [1.11-1.86] | 1.44 [1.11-1.87] |
| **Shushan et al. 1996**[a]<br>**686 (235)** | Not included | 2.00 [1.11-3.60] | Not included |
| **Tzonou et al. 1993**[a]<br>**389 (189)** | 1.05 [0.28-3.98] | 1.05 [0.28-3.96] | 1.05 [0.28-3.94] |
| **Whittemore et al. 1988**[a]<br>**727 (188)** | 1.36 [0.91-2.04] | 1.40 [0.98-2.00] | 1.45 [0.81-2.60] |
| **Wong et al. 1999**[a]<br>**1155 (462)** | 1.00 [0.80-1.30] | 0.92 [0.24-3.57] | 1.00 [0.80-1.25] |
| **Wu et al. 2009**[a]<br>**1297 (609)** | Not included | Not included | 1.53 [1.13-2.07] |
| **Wu et al. 2015**[a]<br>**4092 (1701)** | 1.46 [1.27-1.69] | 1.32 [1.14-1.52] | 1.46 [1.27-1.68] |
| **Gates et al. 2010**[b]<br>**108870 (797)** | 1.06 [0.89-1.28] | Not included | Not included |
| **Gertig et al. 2000**[b]<br>**78630 (307)** | Not included | 1.09 [0.86-1.38] | 1.09 [0.86-1.38] |
| **Gonzalez et al. 2016**[b]<br>**41654 (154)** | 0.73 [0.44-1.20] | 0.73 [0.44-1.20] | 0.73 [0.44-1.21] |

| Reference<br><br>Total sample size (# cases) | OR [95% CI]<br><br>(Berge et al. 2018) | OR [95% CI]<br><br>(Penninkilampi and Eslick 2018) | OR [95% CI]<br><br>(Taher et al. 2019) |
|---|---|---|---|
| **Houghton et al. 2014**[b]<br>**61285 (429)** | 1.06 [0.87-1.28] | 1.12 [0.92-1.36] | 1.12 [0.92-1.36] |
| **Overall OR** | **1.22 [1.13-1.30]** | **1.31 [1.24-1.39]** | **1.28 [1.20-1.37]** |

Abbreviation: CI, confidence interval.
[a] Case-control study
[b] Cohort study

*Evaluation of causation*

The Hill considerations are a set of factors (i.e., strength, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experiment and analogy) that can form a framework for evaluating evidence in humans to help determine whether observed associations may be causal (Hill 1965; Cogliano et al. 2004; U.S. EPA 2005; Fedak et al. 2015).

Established several decades ago, the Hill considerations continue to be employed today, with some modified interpretations; there is general consensus that some factors hold more weight than others. Strength, consistency and biologic gradient are most frequently considered. Conversely, experiment, analogy and specificity are often considered to be less significant, or to hold less weight, in the decision-making framework (Grimes and Schultz 2002; Carson 2018; Kane 2018; Moorman 2018; Singh 2018; Smith 2018; Wolf 2018; Ballman 2019; Diette 2019; Merlo 2019). Temporality, namely that exposure precedes the disease, is another factor that is rarely elaborated upon as it is crucial for the determination of a causal relationship and therefore seldom warrants further discussion. In addition to these factors, other elements such as bias, chance, error and confounding are also important. The likelihood of a causal association is strongest when these elements can be minimized (Hill 1965; Weed and Gorelic 1996; Cogliano et al. 2004; Franco et al. 2004; U.S. EPA 2005; Fedak et al. 2015).

In relation to perineal talc exposure and ovarian cancer, strength, consistency, biological gradient and biological plausibility are discussed below.

<u>Strength</u>

Strength of association is typically a consideration of the relative risk (or OR) between the chemical exposure and the disease. A large risk increases confidence of a causal relationship; however, risks of lower magnitude do not preclude a positive association and rather, may represent a low level of exposure or a rare disease (Hill 1965; Cogliano et al. 2004). The pooled ORs from available meta-analyses ranged from 1.22 to 1.35 (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018;

Penninkilampi and Eslick 2018; Taher et al. 2019), which would not be considered "large." However, the results for the pooled analyses are statistically significant, with narrow confidence intervals. As noted in Table 7-1, a high proportion of available case-control studies representing a broad section of the population have reported strikingly similar ORs. Ovarian cancer is recognized as a rare disease (AICR 2020; CTFPHC 2020; NCI-SEER 2020) and, as such, the large number of studies giving similar results is noteworthy.

Some authors argue that the small strength of association (OR approximately 1.3) can be explained by bias and/or confounding (see *Bias and confounding* section below) and is therefore not an indication of causation (Diette 2019; Merlo 2019; Moore 2019). Others, while not disputing that the association is modest, argue that the factor has been satisfied as an indication of causation (Kane 2018; Moorman 2018; Siemiatycki 2018; Singh 2018; McTiernan 2019). Moorman (2018) and Smith-Bindman (2018) contend that perineal talc use is common among women in the epidemiological studies and therefore even a modest increase in risk is of concern to the population. Ballman (2019) raises the argument that such statements assume that the association is causative.

Strength and consistency of association are two factors often considered together. The replication of results seen across multiple studies supports strength (Singh 2018). The measured ORs (1.22 to 1.31) are modest, but they are also similar and unlikely to be random. Considering that ovarian cancer is rare, and therefore that a large data set is required to detect an association, the findings in the available literature are significant.

Consistency

As described by Hill (1965), consistency considers whether the observed association has been replicated by different people, in different places, under different circumstances and at different times. The epidemiological studies examined in the meta-analyses were conducted over different time periods (across more than four decades), among different ethnicities, and spanned many cities/communities/countries worldwide (Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2019). The pooled ORs calculated in the three most recent meta-analyses, 1.22 (Berge et al. 2018), 1.31 (Penninkilampi and Eslick 2018) and 1.28 (Taher et al. 2019), which suggest a 22% to 31% increase in risk, are consistent with those calculated in older studies, i.e., 1.33 (Huncharek et al. 2003), 1.35 (Langseth et al. 2008) and 1.24 (Terry et al. 2013). As highlighted in Table 7-1, a high percentage (91%) of the epidemiology studies examined had ORs greater than the null (1.0) and overall consistent values despite being conducted by different authors using varied methodologies. The general direction and strength of the association is consistent (Singh 2018). Several of the individual values lack statistical significance; however, given the rarity of ovarian cancer, many of the available human studies may not be sufficiently powered to detect a low OR; sample sizes were often not large enough to detect a 20% to 30% increase in risk, even when pooled (Narod 2016; McTiernan 2019, O'Brien et al. 2020).

Measures of consistency,[13] i.e., quantification of heterogeneity, have been reported in two of the recent meta-analyses and support the view that that the results across the epidemiological studies are consistent (Penninkilampi and Eslick 2018; Taher et al. 2019). However, the disproportionate number of case-control studies versus cohort studies may affect this significance (Ballman 2019).

Greater consistency across the different study types (cohort vs case-control designs) would increase the likelihood of a causal relationship. The major disadvantage of case-control studies is that they can be prone to recall bias. Cohort studies minimize selection and recall biases, but they require long follow-up times and a large number of participants, in particular for rare outcomes, in order to achieve requisite power. Since cohort studies require these additional resources, they also tend to target multiple research questions to gather information on several exposures and outcomes (Celentano and Szklo 2019). Specific to talc and ovarian cancer, some recent analyses have given precedence to the results of the cohort studies, arguing that they provide stronger evidence for an association than case-controls (Ballman 2019; Moore 2019; Goodman et al. 2020; Johnson & Johnson Consumer, Inc. 2020). Other analyses support the view that such generalizations cannot be made and that there are many factors affecting the validity of a study regardless of design (Moorman 2018; Siemiatycki 2018; Smith-Bindman 2018; McTiernan 2019).

The available cohort studies did not demonstrate the same level of statistical significance as was seen in the case-control studies. Perspectives vary among authors with respect to statistical significance: some (Diette 2019; Merlo 2019; Moore 2019) regard it as critical, whereas others (Narod 2016; Siemiatycki 2018; McTiernan 2019) argue that it is not. A recent paper by Amrhein et al. (2019) argues that “a statistically non-significant result does not ‘prove’ the null hypothesis.” A confidence interval that contains the null value often also contains non-null values of importance and should not be used to conclude that there is no association; values just outside the interval are not substantially different from those within the interval. Ovarian cancer is expected to have a long latency period, with estimates of 15 to 40 years (Purdie et al. 2003; Gonzalez et al. 2016; Tran et al. 2019). It is not known whether the follow-up periods in the cohort studies were adequate to detect a potential association between perineal talc exposure and ovarian cancer. As cited above, the cohorts, even when pooled together, may not be sufficiently powered. Cohort studies are less desirable than case-control studies for

[13] $I^2$ represents the percentage of variation across studies that is due to heterogeneity rather than chance; an $I^2$ of 0% represents no heterogeneity and larger $I^2$ values indicate increasing heterogeneity (Higgins et al. 2003). Penninkilampi and Eslick (2018) used Cochran’s Q statistic to derive an $I^2$ statistic of 10.52% for any perineal use, where $I^2$ = 25% is considered low heterogeneity and 50% would be considered moderate. Taher et al. (2019) also conducted a heterogeneity test and reported an $I^2$ = 33% for ever vs never talc use.

rare diseases because case-control studies can generate a much larger number of cases. Referring to Table 7-1, the number of cases (797) in the largest cohort study (Gates et al. 2010) is considerably lower than the number of cases (2041) in the largest case-control study (Cramer et al. 2016), whereas the sample sizes are considerably larger in the cohort study, namely 108 870 compared to 4141 in the case-control study (Bindman 2018; Penninkilampi and Eslick 2018; Singh 2018; Celentano and Szklo 2019;). Related to adequacy of follow-up time is the age of participants in the cohort studies. The median age of ovarian cancer diagnosis is 63 (NCI-SEER 2020). In the O'Brien et al. (2020) analysis, two of the cohorts (NHS II and SIS) representing nearly 40% of the sample size are made up of younger populations, with many of the individuals at or below the median age of diagnosis, indicating that cancer incidences may not yet be detectable. At least some of the cohorts may still be too recent and limited to illustrate the true outcome of a rare disease.

None of the cohort studies accounted for both sufficient follow-up time and comparable exposure groups. Diette (2019) and Merlo (2019) note the idea that the cohort studies could sufficiently account for the latency of ovarian cancer since powder use likely started long before the beginning of the study. Other limitations of the cohort studies include the following:

- The questions regarding powder use were only administered once, and in several cases not until several years following the initiation of the study, which could bias the findings towards null (Moorman 2018; Singh 2018, McTiernan 2019; O'Brien et al. 2020). Ballman (2019) also recognizes this as a limitation but considers it to be minimal since the duration of powder use among ever-users can be extensive (> 20 years).
- The cohort studies all limited their subjects considerably (e.g., post-menopausal, a sister with breast cancer, registered nurses) and may not represent the general population. O'Brien et al. (2020) recognizes that collectively, these cohorts are predominately white, highly educated and not obese, which could limit generalizability.
- The question related to powder use was often not specific to talc and could have included other powders, which could bias the findings towards null (Singh 2018; Tran et al. 2019). Smith-Bindman (2018) and McTiernan (2019) suggest that differences in exposure measurement and specificity of study design may explain the apparent discrepancy in results between the case-control and the cohort studies. For example, cohort studies only measured exposure at study entry and were designed to look at several exposures and diseases, while most case-control studies were designed to specifically address perineal talc use and ovarian cancer risk.

Over 90% of the studies examined (case-control and cohort) calculated a positive association between talc use and ovarian cancer. Consistent values were recorded, with overall ORs from the recent meta-analyses ranging from 1.22 to 1.31. It is recognized that there is some inconsistency between results from case-control studies versus cohort studies, in particular with respect to the degree of statistical significance.

However, this could be explained by the limitations of the cohort studies described above. Overall, there is a high degree of consistency in the epidemiological studies across several decades conducted in different parts of the world.

Biological gradient

Being able to support a biological gradient or dose-response relationship is another important factor in establishing causation. Some authors suggest that the available data show no clear or consistent trend with respect to dose (e.g., frequency, duration of use) and response (Ballman 2019; Diette 2019; Johnson & Johnson Consumer, Inc. 2020). However, several studies (Harlow et al. 1992; Terry et al. 2013; Cramer et al. 2016; Schildkraut et al. 2016; Gabriel et al. 2019) do suggest a trend of increased OR with increased cumulative exposure. Meta-analyses conducted by Berge et al. (2018) and Penninkilampi and Eslick (2018) report a weak trend with duration and frequency of genital talc use and a slight association with respect to length of talc use, respectively. Taher et al. (2019) isolated seven studies that provided some evidence of increased risk of ovarian cancer with increasing perineal applications of talc; however, none demonstrated both a clear dose-response trend and statistical significance. Several of these studies are cited by the authors as evidence in support of biological gradient, but the limitations of the available data prevented this factor from contributing heavily to the decision making framework (Moorman 2018; Siemiatycki 2018; Singh 2018; Smith-Bindman 2018; Wolf 2018; McTiernan 2019). McTiernan (2019) notes that a typical dose-response relationship may not be necessary since ovarian talc particle burden may not be associated with the number of applications; it may be a substance where there is no safe dose. Similarly, Terry et al. (2013) noted that the association may not be linear. Many of the studies only assessed a single dose level (ever-users vs never-users). Furthermore, data with respect to the types of powder used by subjects or the amounts applied were not presented, and therefore a relationship between the concentration/dose of talc in the powder and the incidence of ovarian cancer could not be investigated.

Collectively, there is significant exposure information lacking to permit a fulsome assessment of biological gradient.

Biological plausibility

According to Hill (1965), biological plausibility is helpful to determine causality but is “a feature that cannot be demanded.” Particles of talc are able to migrate into the pelvis and ovarian tissue, possibly causing irritation and inflammation. Although a specific order of events by which perineal talc exposure could lead to ovarian cancer has not been established, several recent publications (Campion et al. 2018; Fletcher et al. 2019; McDonald et al. 2019a; McDonald et al. 2019b; Mandarino et al. 2020) support the hypothesis that perineal talc exposure leading to ovarian cancer is biologically plausible. Several authors (Kane 2018; Moorman 2018; Siemiatycki 2018; Singh 2018; Smith 2018; McTiernan 2019) agree that the factor of biological plausibility has been met,

even in the absence of many of the recent studies which would not have been available at the time of their analyses. Building from ideas introduced by Hill (1965), these authors suggest that biological plausibility depends on current state of scientific knowledge and should not rest on demonstrated proven mechanisms to consider this factor “satisfied”, but rather whether the hypotheses “make sense” or are scientifically possible. Siemiatycki (2018) provides several examples from the history of medicine and epidemiology where associations were demonstrated as causal long before the mechanisms were validated. Others authors, however, argue that the factor has not been met or has only weakly been satisfied or that theories are not substantiated (Ballman 2019; Diette 2019; Moore 2019; Neel 2019). Ballman (2019) suggests that since the ability to predict plausibility has advanced, the expectations of “sounding reasonable”, set decades ago, need to be exceeded. These authors reason that there is lack of support in the scientific literature to demonstrate the relationship between perineal users vs non-users and the particle load found in tissues.

The recent study by McDonald et al. (2019b), which likely was not available at the time of the authors’ analyses, does demonstrate increased talc burdens in genital talc users compared to non-users and indicates that there is a high likelihood of sample contamination without extreme measures to control it, suggesting that talc burden in non-users reported in older studies was possibly a result of sample contamination. The assessment by Goodman et al. (2020) did consider recent publications on the mechanistic evidence and concluded that there is insufficient support for any proposed mechanism.

Overall, the available animal and human studies described under *Mode of action* above clearly indicate that particles, including talc, may transfer from the vagina to the fallopian tubes and ovaries following perineal application. Recent research with respect to specific mechanisms (inflammation and/or tumour precursor events) add increased support to the biological plausibility.

Bias and confounding - other elements for consideration

In order to increase the confidence of causal inference, bias, chance, error and confounding need to be ruled out or minimized. There are a range of opinions as to the extent to which these factors may influence the available epidemiological data. Chance is unlikely to play a significant role since the distribution of ORs across the epidemiological studies is not random (McTiernan 2019; Siemiatycki 2018).

There are many unknowns with respect to the causes of ovarian cancer, making it difficult to account for all confounders. Age, race, low parity, infertility, and a family history of certain cancers are among the most likely risk factors in the etiology of epithelial ovarian cancer (Fiume et al. 2015), with age and parity considered key (Taher et al. 2019). Most of the human epidemiology studies reported effects adjusted for a variety of these potential confounders. It is possible that one or more confounders exist and may be at play in the epidemiological studies for perineal talc use that have not yet

been recognized as such (Diette 2019; Merlo 2019). Overall, although confounding cannot be definitively excluded, significant efforts have been made to adjust for the recognized confounders.

The possibility of biases and/or errors are recognized throughout the literature. There are potential sources of biases/errors and the impact can differ depending on the study design. In general, case-control studies are more susceptible to biases. Some authors think that these other factors (i.e., bias, confounding, error) are sufficient in the case-control studies to account for the apparent positive association (Ballman 2019; Diette 2019; Merlo 2019; Moore 2019; Goodman et al. 2020; Johnson & Johnson Consumer, Inc. 2020), whereas others, although not disputing the existence of these other factors, conclude that they are unlikely to account completely for the consistent associations produced across the studies (Rosenblatt et al. 2011; Schildkraut et al. 2016; Moorman 2018; Siemiatycki 2018; Singh 2018; McTiernan 2019).

Recall bias, unique to case-control studies, is of note with respect to perineal talc use and ovarian cancer. Recall bias occurs when individuals in a study tend to have a more vested interest and over-report the retrospective exposure, leading to potential over-estimation of risk. Conversely, the controls may under-report. Some authors (Cramer 2016; Narod 2016; Berge et al. 2018; Penninkilampi and Eslick 2018; Siemiatycki 2018) argue that recall bias does not factor strongly in the case of perineal talc exposure and risk of ovarian cancer. In studies where the exposure is simple (e.g., never- vs ever-use), recall bias is unlikely to be an important source of bias (Narod 2016). According to Penninkilampi and Eslick (2018), the potential for recall bias can be decreased when the exposure of interest (i.e., talc use) is part of a more extensive questionnaire, as is the case for many of the studies. Cramer et al. (2016) conducted a sensitivity analysis and determined there was an approximate 18% buffer to account for recall bias before the results of the study would be nullified; however, it could not be substantiated whether this is a reasonable buffer.

Recall bias can also be influenced by increased media attention (Muscat and Huncharek 2008; Penninkilampi and Eslick 2018). One recent case-control study in particular (Schildkraut et al. 2016) supports this, in which the calculated ORs for subjects interviewed after 2014, when lawsuits around talc and ovarian cancer were in the media, were considerably higher compared to those for subjects interviewed prior to 2014. However, looking at Table 7-1, the majority of the case-control studies used in the meta-analyses were conducted prior to this media attention, and the calculated ORs from the more recent studies are lower than many of those conducted much earlier. Two of the recent meta-analyses (Berge et al. 2018; Penninkilampi and Eslick 2018) used funnel plots as a mechanism to assess publication bias and reported an absence of concern.

<u>Ovarian cancer – weight of evidence</u>

There are no adequate animal models available to assess ovarian cancer risk due to perineal talc exposures. The animal models available do, however, note an inflammatory response in the reproductive tract of rodents exposed to talc particles. As well, recent research with respect to specific mechanisms add increased support to the biological plausibility, consistent with the possible human mode of action data for cancer development. The human database provides differing results between case-control and cohort studies. There is, however, support for the idea that despite greater susceptibility to biases, case-control designs are well suited to study perineal talc exposure and ovarian cancer. Furthermore, the available cohort studies are not without limitations. Overall, there is a high degree of consistency in the epidemiological studies across several decades conducted in different parts of the world. Although there are uncertainties related to bias, there is confidence in the robustness of the available database for use in characterizing ovarian cancer risk attributed to talc exposure. Furthermore, the available data are indicative of a causal relationship.

## 7.2 Exposure assessment

This exposure assessment focuses on routes of exposure where critical effects have been 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.

### 7.2.1 Environmental media, food and drinking water

Talc is a naturally occurring mineral, and there are several deposits in Canada (Kogel et al. 2006). Currently, there is one operating open-pit mine and concentrator, along with an operating mill (MAC 2019). However, no talc concentration data in ambient air or around open-pit talc mines and processing facilities have been reported. Although particulate matter data for inhalable and respirable particles are available in the vicinity of these facilities (NPRI 2018), they were not used in the exposure assessment as particulate matter released from facilities is expected to contain a mixture of substances and therefore the concentration would not reflect talc exposure from this source. Given the limited number of industrial and commercial sites producing and processing talc in Canada, talc exposure from ambient air is not expected to be significant.

Talc is insoluble in water (Table 3-1) and is expected to settle out during water treatment. Exposure to the general population from drinking water is not expected.

There is potential for oral (i.e., dietary) exposure resulting from the use of talc as a food additive, but exposure from these uses is expected to be minimal (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 27, 2018; unreferenced). Dietary exposure from the use of talc as a component in the manufacture of some food packaging materials is expected to be negligible and dietary

exposure is not expected from its use as a component in the manufacture of incidental additives (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 27, 2018; unreferenced). Exposure from the oral route was not quantified because no critical health effects from the oral route of exposure have been identified. The JECFA has assigned an ADI of “not specified” for talc on the basis of low toxicity, and talc is considered “generally recognized as safe” for specific uses in food packaging in the United States (JECFA 2006; U.S. FDA 2019a, b).

### 7.2.2 Products available to consumers

As of 2020, talc is present as a medicinal or non-medicinal ingredient in approximately 10 000 self-care products in Canada, including approximately 150 non-prescription drugs, approximately 2100 NHPs, and approximately 7750 cosmetic products. In addition, there are approximately 1400 prescription drugs containing talc. There is therefore potential for oral exposure to talc resulting from the use of such products. However, exposure from the oral route was not quantified as no critical health effects from the oral route of exposure have been identified.

There is the potential for dermal contact with talc from the use of self-care products. Systemic exposure resulting from dermal contact with talc is expected to be negligible, as it is not expected that talc will be absorbed on the basis of its physical-chemical characteristics as an insoluble solid particle. In addition, a dermal health effect endpoint has not been identified for talc.

Notifications submitted under the *Cosmetic Regulations* to Health Canada for talc, the LNHPD (modified 2018), the Drug Product Database (DPD) (modified 2018), voluntary information submitted to Environment and Climate Change Canada and Health Canada (ECCC, HC 2017), publicly available databases and websites (e.g., Household Products Database 1993- ; CPCat 2014; CPID 2017), and material safety and technical datasheets were used to identify products where there is: (a) the potential for inhalation of insoluble respirable talc, and (b) the potential for exposure to the perineal region. These products and associated exposures are presented below.

No inhalation or perineal exposures for the general population were identified with respect to the major commercial or industrial uses of talc in paper, plastics, ceramics, and putties.

#### Inhalation exposure

Potential inhalation exposures were focused on products that were formulated as loose powders and were available to consumers, which included approximately 400 self-care products (primarily cosmetics). Available information of interest were self-care products marketed as cosmetics, natural health products, or non-prescription drugs that are intended for application to the body, face, eyes, lips, nails, feet, buttocks (babies), and

hair. The primary uses are as makeup, moisturizers and cleansers and to a lesser extent as antiperspirant/deodorants, hair removal products, dry hair shampoo, hair colour and nail polish. Concentrations of talc range from less than 10% to 100% in these types of products. Products formulated as pressed powders, which comprise the majority of cosmetics containing talc (approximately 5300 products), were not identified as a potential source of inhalation exposure of concern because these formulations contain coarser particles and binders, such as oils or waxes, which help bind the particles together and do not lead to the formation of a “dust cloud” available for inhalation.

Airborne inhalable and respirable-sized talc particles (≤ 10 µm and 4 µm, respectively) have been measured during the use of baby and body powders in several studies (Aylott et al. 1979; Russell et al. 1979; Anderson et al. 2017; Rasmussen et al. 2019). In order to confirm the size of talc particles in loose powder self-care products, Health Canada measured the particle-size distribution of four products (one baby powder, two adult body powder products, and one loose face powder) containing high concentrations of talc (> 90%) available in Canada (Rasmussen et al. 2019). Using the Aerodynamic Particle Sizer (APS; TSI Inc. Model 3321), the particle-size distribution for the four products was determined to range from < 1 to 8 µm, with median particle sizes ranging from 1.7 to 2 µm (Rasmussen et al. 2019). Thus, all of the particles were within the thoracic size fraction of inhalable particles (≤ 10 µm), and the median particle size was within the respirable range (≤ 4 µm), i.e., small enough to penetrate deep into the respiratory tract. Number concentrations measured using a scanning mobility particle sizer (SMPS; TSI Inc. Model 3788/3082) indicated that the proportion of nano-sized particles (< 100 nm) was small (< 10%) to negligible, depending on the product.

Several studies were conducted in the 1970s to provide data required to assess the safety of talc powder products and measure air concentrations (Pooley 1972; Aylott et al. 1979; Russell et al. 1979). These studies demonstrated that during the use of face, baby, and adult powders, there are quantifiable concentrations of respirable talc particles available for inhalation exposure. In 1972, Pooley measured respirable talc concentrations using gravimetric dust samplers in the breathing zone of infants and adults during diapering activities. Average respirable concentrations were the same for infants and adults at 8 mg/m$^3$. The median size of respirable particles was approximately 1.74 µm. In a 1979 study, Aylott et al. determined mean respirable air concentrations of 0.48 to 1.9 mg/m$^3$ of talc (< 7 µm) over 5 minutes for loose face powder, adult dusting powder, baby dusting powder, and micronized adult dusting powder (Aylott et al. 1979). That same year, concentrations of talc (≤ 10 µm) of 0.19 and 2.03 mg/m$^3$, respectively, were determined near the infant breathing zone during a simulation of routine application of talcum powder during diapering and in the breathing zone of adults during the application of talcum powder to their body (Russell et al. 1979). In both Aylott et al. (1979) and Russell et al. (1979), the highest air concentrations were associated with the adult application of talcum powder to their bodies over infant diapering and application of loose facial powder. There are uncertainties with the calculated talc concentrations determined from these studies due

to limitations in the collection and analysis of talc concentrations resulting from the use of older personal air sampling and cyclone collecting equipment and methods used to quantify the concentration of talc in air (i.e., extrapolating from Mg measured using atomic absorption spectrometry (AAS), weight measurement on an early prototype quartz crystal mass monitor, conversion of gravimetric data to number concentrations).

In 2017, a study assessing the health risk from the use of cosmetic talc from historical products was published (Anderson et al. 2017). It examined talc products believed to have been manufactured and sold during the 1960s and 1970s to characterize airborne respirable dust concentrations during the use of these products. To quantify respirable talc concentrations in the breathing zone, five volunteers were asked to apply talc products as they typically would in a bathroom setting. Cyclone air sampling devices capturing $PM_4$ were attached to the breathing zone of each volunteer. Each exposure simulation consisted of eight application events, at 6-minute intervals, for a total sampling duration of 48 minutes. This study design ensured that the sample mass on the sampling filter was large enough for quantification and accuracy, but it was not expected that individuals apply talc every 6 minutes over a 48-minute window during the typical use of a talc body powder. Average talc concentrations over the 48-minute exposure simulation were calculated using the total measured mass (from eight applications over 48 minutes) and the air volume over the entire 48-minute sampling period. Respirable talc concentrations ranged from 0.26 to 5.03 $mg/m^3$, and the average was 1.46 $mg/m^3$. The average air concentration by subject ranged from 0.44 to 3.28 $mg/m^3$. Respirable talc concentrations were more variable among all subjects and between subjects than per individual subjects, suggesting that individual behaviour and use patterns have a strong influence on airborne concentrations.

In 2018, Health Canada conducted a small study to measure air concentrations of particles in the breathing zone of adult volunteer subjects while they were applying talc-containing self-care products (Rasmussen et al. 2019). Continuous, direct-reading, personal breathing-zone monitors (positioned beside the nose) measured average concentrations of particulate matter of aerodynamic diameter of 4 µm or less ($PM_4$) on the subject of 0.48 ± 0.18 and 1.80 ± 0.82 $mg/m^3$ for volunteers applying body powder (subject A) and loose face powder (subject B), respectively. Subjects repeated the application in triplicate. These average concentrations fall within the range of concentrations measured by Anderson et al. (2017). The application of loose face powder resulted in the highest average air concentration in the immediate vicinity of the nose. A third subject in the study applied talc to a wetsuit prior to donning (subject C); however, this activity was considered to be different than the use of talc as a self-care product. Mean airborne concentrations on subject C of 0.61 ± 0.09 $mg/m^3$ were similar to those on subject A and B. However, the duration of the combined primary and secondary particle cloud was much longer at 700 ± 265 sec (subject C) versus 57 ± 8 sec (subject A) and 65 ± 7 sec (subject B). In this study, the cloud characteristics, concentration and duration varied. The variation may have resulted from the different purposes and methods of applying the talc product and from behavioural and physical differences among the subjects (Rasmussen et al. 2019).

Several exposure scenarios were identified where there was potential for inhalation exposure to talc particles from the use of self-care products, namely the use of baby, body, face, and foot powders (loose formulations) and dry hair shampoo. Although there may be differences in air concentrations of talc associated with the use of different types of self-care products (e.g., baby powder, foot powder), there is insufficient data available to generate reliable air concentrations for each use which would capture variability within and between subjects. Therefore, average air concentrations by subject from Anderson et al. (2017) were combined with the body and face powder replicates from Rasmussen et al. (2019) to obtain an overall average air concentration of 1.36 ± 0.97 mg/m$^3$ available for inhalation exposure during the use of self-care products (Appendix A, Table A-1). Anderson et al. (2017) and Rasmussen et al. (2019) were considered to provide the best and most relevant available data as they not only utilized current collection instruments for air sampling and modern methods for quantifying talc but also presented data by subject, which was important as the variability among and between subjects is higher than within individual subjects and the combined sample size is relatively low to capture variability across the population (n = 7). The average air concentration value of 1.36 mg/m$^3$ was used to estimate adjusted air concentrations for self-care products based on the highest concentration of talc present in these products. The results are summarized in Table 7-2. The inputs for each of these scenarios are outlined in Appendix A (Table A-2). Exposure to talc during application of loose powders on the eyes, lips and nails is expected to be lower than the estimates presented in Table 7-2 due to the smaller quantity of product applied and smaller area of application. Exposure to talc during the use of loose powder hair colour is expected to be similar to or lower than use of talc as a dry hair shampoo.

**Table 7-2. Inhalation exposure estimates to talc from self-care products available to consumers**

| Product type | Age group | Average concentration in air per event (mg/m$^3$)[a] | Higher tier adjusted exposure concentration (mg/m$^3$)[b] |
|---|---|---|---|
| Baby powder 100% talc | Infant and adult | 1.36 | 0.0071 |
| Body powder 100% talc | Adult | 1.36 | 0.0047 |
| Face powder 100% talc | Adult | 1.36 | 0.0047 |
| Foot powder 97% talc | Adult | 1.32 | 0.0034 |
| Dry hair shampoo 100% talc | Adult | 1.36 | 0.0011 |

[a] Average measured air concentrations (Anderson et al. 2017, Rasmussen et al. 2019) × the highest concentration of talc in product type.
[b] Refer to Appendix A, Table A-2 for details.

### Perineal exposure

Several types of self-care products containing up to 100% talc are used in the perineal region of the body to reduce moisture and odour. Adult body powders used in the perineal region for feminine hygiene practices are still available on the Canadian market, although there has been a decline in this use over time (Houghton et al. 2014; Narod 2016). Baby powder products containing up to 100% talc are used in the perineal region of infants during diapering. In addition, there are a small number of diaper or rash cream self-care products (fewer than 10) for use in the perineal region which contain low concentrations of talc as a non-medicinal ingredient. Talc is permitted as a medicinal ingredient in diaper rash products at concentrations from 45% to 100% (Health Canada 2018). However, there are no diaper rash products listed in the LNHPD (modified 2018) containing talc as a medicinal ingredient.

Additional self-care products that have the potential for perineal exposure include antiperspirants and deodorants (e.g., genital antiperspirants), body wipes, bath bombs and bubble bath, and to a lesser extent (due to wash off or removal) other bath and shower products (i.e., soap, wash/gel, scrub) and products associated with hair removal (e.g., epilatory products). These products are formulated as gels, sprays, loose powders, and solid cakes and range in concentration from less than 1% to 100% talc.

As indicated in Section 4, there is no evidence to suggest that talc is currently being used as a dry lubricant on condoms or medical examination gloves in Canada. At present, these are not considered to be sources of perineal exposure.

While there are known sources of perineal exposure to talc, the available literature does not permit a quantitative assessment of perineal exposure from the use of self-care products.

## 7.3 Characterization of risk to human health

Consistent with other international regulatory and advisory bodies (Danish EPA, U.S. EPA, MAK-Commission, U.S. FDA, and JECFA), no critical health effects were identified for talc via the oral or dermal routes of exposure. As such, oral exposures to talc resulting from food intake and oral and dermal exposure from the use of self-care products are not of concern.

Considering available lines of evidence, critical health effects have been identified following inhalation exposure to respirable talc particles. The available health effects data are adequate and study outcomes are consistent in providing a high degree of confidence in the assessment of health outcomes following inhalation exposure to talc particles. From the available toxicological studies, a NOAEC of 2 mg/m$^3$ from the NTP inhalation studies in mice and rats was identified in which non-cancer lung effects, with lung overload, were noted at the next highest concentration of 6 mg/m$^3$.

Using a lower-tier assessment approach, a small margin of exposure (MOE) of 1.5 was obtained through the comparison of the NOAEC of 2 mg/m$^3$ to the average talc air concentration of 1.36 mg/m$^3$ following the use of a loose powder self-care product. Additional refinements were applied taking into consideration the differences in exposure duration between the exposure scenario and the animal study to incorporate into a higher-tier assessment. The NOAEC is derived from an animal study with an exposure duration of 6 hours per day, 5 days per week, over 4 weeks, while the actual exposure scenarios from the use of self-care products are intermittent, occurring in minutes per day, daily, or weekly over many years.

To address this difference, both the NOAEC (2 mg/m$^3$) and the talc air concentration (1.36 mg/m$^3$) were adjusted to a continuous exposure scenario according to U.S. EPA guidance on inhalation risk assessment to more accurately characterize potential risk (U.S. EPA 1994, 2009). The NOAEC of 2 mg/m$^3$ is equivalent to an adjusted concentration of 0.36 mg/m$^3$, as noted in the *Health effects* section. The NOAEC of 2 mg/m$^3$ was extracted from a 4-week inhalation study as a NOAEC for chronic exposure was not available. The measured talc air concentration (1.36 mg/m$^3$) from the use of self-care products was also adjusted to a continuous exposure scenario (higher-tier assessment) as presented in Table 7-3 (for further details see Appendix A, Table A-2). Episodic exposures from product use are expected to increase lung load due to the long alveolar clearance of talc.

**Table 7-3. Relevant exposure and hazard values for talc, and margins of exposure, for determination of risk**

| Exposure scenario | Adjusted air concentration, CA (mg/m$^3$)[a] | Adjusted critical-effect level (mg/m$^3$) | Critical health effect endpoint | MOE |
|---|---|---|---|---|
| Baby powder 100% talc | 0.0071 | NOAEC[adj]: 0.36 | non-cancer lung effects | 50 |
| Body powder 100% talc | 0.0047 | NOAEC[adj]: 0.36 | non-cancer lung effects | 76 |
| Face powder 100% talc | 0.0047 | NOAEC[adj]: 0.36 | non-cancer lung effects | 76 |
| Foot powder 97% talc | 0.0034 | NOAEC[adj]: 0.36 | non-cancer lung effects | 106 |
| Dry hair shampoo 100% talc | 0.0011 | NOAEC[adj]: 0.36 | non-cancer lung effects | 327 |

Abbreviations: adj, adjusted; CA, concentration in air per event; MOE, margin of exposure.

[a] Measured air concentrations from Anderson et al. (2017) and Rasmussen et al. (2019) (see Table A-1 for details) based on the highest concentration in products. See Table A-2 for details on adjusted air concentrations. For most of these product types, there is a wide range of talc concentrations (< 10% to 100%).

The margins of exposure (MOEs) between the adjusted critical effect level and the adjusted air concentrations range from 50 to 327 for self-care products. The MOEs for baby powder, body powder and loose face powder are considered potentially inadequate to account for uncertainties in the health effects (including the use of a short-term study due to a lack of a NOAEC from chronic studies) and exposure databases. The MOEs for dry hair shampoo and foot powder are considered adequate to address uncertainties in the health effects and exposure databases.

Based on the available data, ovarian cancer was identified as a critical health effect for the perineal route of exposure to talc. While animal models are generally inadequate to assess ovarian cancer risk, the available animal studies (noting inflammatory response to talc and the ability of talc particles to migrate up the reproductive tract) support biological plausibility and results were consistent with a possible human mode of action for cancer development. The database is large, and while cohort and case-control studies generally gave different results, the overall database provides adequate information to assess the risk of ovarian cancer due to talc exposure. There is the potential for perineal exposure to talc from the use of various self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs, bubble bath). Characterization of ovarian cancer risk is qualitative in nature as a clear dose response for ovarian cancer could not be derived from the available literature. Data from meta-analyses of epidemiological studies indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer (Huncharek et al. 2003; Langseth et al. 2008; Terry et al. 2013; Berge et al. 2018; Penninkilampi and Eslick 2018; Taher et al. 2019). Although some authors note concerns with regard to bias in the literature, considering the available lines of evidence, the current data are indicative of a causal effect. Given that there is the potential for perineal exposure to talc from the use of various self-care products, a potential concern for human health has been identified.

## 7.4 Uncertainties in evaluation of risk to human health

The inhalation of talc has been associated with a variety of non-cancer lung effects, commonly termed talcosis. Dose-response data for lung effects in humans are, for the most part, lacking, and the use of animal data to quantify risk due to talc inhalation is considered appropriate. Despite the lack of exposure quantification, there are numerous case reports, as well as worker studies, that have identified non-cancer health effects from inhalation of talc powders. As there are no adequate long-term inhalation toxicity studies in animals, there is some uncertainty regarding the extrapolation of the NOAEC identified in animal models exposed for 6 hours per day for a short duration (4 weeks) to

long-term episodic human exposures. The true NOAEC for chronic exposure in test animals is likely substantially lower than 2 mg/m$^3$.

There is some uncertainty in using combined air concentrations from adults applying body powders and adults applying face powder as surrogate data for infants during diapering, adults during diapering, and adults applying foot powder and dry hair shampoo. Aylott et al. (1979) found air concentrations in the breathing zone of infants during diapering to be approximately 10-fold lower than adults during diapering activities. However, in studies conducted by NIOSH (Dement et al. 1972) and Pooley (1972), air concentrations in the breathing zone of infants were similar to, or in some cases higher than, adults who were diapering infants. The best and most relevant available data were used to derive air concentrations of talc during the use of self-care products.

Some self-care products, and in particular some face powders, may contain a cover or another mechanism that could reduce either the potential for the generation of a particle or dust cloud or the concentration of the dust cloud during use of the product. There is uncertainty as to which products on the market, if any, incorporate these exposure-mitigation measures and the proportion of such products.

There is also some uncertainty regarding the use of talc diaper rash products on broken or abraded skin, where talc penetration may occur, in contrast to use on healthy skin. The CIR Expert Panel (2013) concluded that “talc should not be used on skin where the epidermal barrier is removed or on skin that has greater than first degree burns.” However, typical diaper rashes are unlikely to reach the severity described.

Ovarian cancer, in general, is not well understood, and a comparable animal model is not available. The available human studies on possible migration of talc to the ovaries and presence of talc particles in the ovaries are indicative but not definitive. Limitations of these studies include the fact that particles are administered in solution, that particles are inserted into reproductive tract channel, and that the studies are conducted on patients undergoing elective surgery (perhaps under anesthesia, in the supine position and/or not of healthy status). The studies available also did not assess long-term exposure, with most only examining one or a few administrations. In general, there was a lack of studies that investigated long-term perineal talc exposure in a healthy individual.

There are also limitations with the human epidemiological data. There are a range of opinions in the literature as to whether ovarian cancer should be analyzed as a whole or divided into specific subtypes. Information is also lacking with respect to the exposure in the epidemiological studies. The questions asked of participants in the epidemiological studies were not always specific to talc-containing powders, and even when the questions were more detailed, participants may make assumptions or not specifically recall whether they used talc-based formulations. If “users” were actually users of talc-free powders, this could falsely bias results towards the null (Singh 2018; Tran et al.

2019). There is uncertainty as to whether, or how much, bias and confounding may have factored into the cohort and case-control studies. There is also uncertainty around possible selection bias in the epidemiological studies. Both case-control and cohort designs are susceptible to selection bias, which can bias the results in either direction. It is possible that the selection of participants is not representative of the entire target population and/or that the cases versus controls (or exposed versus unexposed) within a study differ from one another. The response rates and exclusion criteria can also contribute to selection bias as it is not known how results would be affected if all potential subjects had actually participated (Singh 2018; Ballman 2019; Merlo 2019; Goodman et al. 2020). While there may not be consensus within the scientific community regarding the interpretation of the epidemiological information, after weighing the available lines of evidence, the assessment determined that the current data are indicative of a causal effect.

It is also possible that the identified cancer incidences are specific to loose powder formulations. However, there is limited information on cancer incidences and other formulation types (e.g., creams). Health Canada has identified self-care products with the potential for perineal exposure (e.g., baby powder, body powders, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs, bubble bath), but there is no indication exactly how the products are being used, the extent to which they would contribute to perineal exposure, or with what frequency and amount.

Talc use during diapering has not been adequately addressed in the literature. It has not been determined whether the internal female genital tract is exposed to talc dusts during infancy (Muscat and Huncharek 2008) or how long the insoluble particles may remain in human reproductive tract tissues. This may impact the calculation of risk from case-controlled studies if cases of women who self-identify as “never-users” were in fact exposed as infants through diapering.

Similarly, whether inhalation of talc particles could result in ovarian exposure due to lymphatic transfer of particles or whether responses may be immune-mediated has not been adequately investigated for use in mode of action analysis.

# 8. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from talc. It is concluded that talc does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Considering all the information presented in this screening assessment, it is concluded that talc meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter

the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that talc meets one of the criteria set out in section 64 of CEPA. It has also been determined that talc meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

# References

[AICR] American Institute for Cancer Research. World Cancer Research Fund. Worldwide cancer data. [accessed 2020 July].

Akira M, Kozuka T, Yamamoto S, Sakatani M, Morinaga K. 2007. Inhalational talc pneumoconiosis: radiographic and CT findings in 14 patients. Am J Roentgenol. 188(2):326-333.

American Academy of Pediatrics. 2015. Make Baby's Room Safe: Parent Checklist. Adapted from Caring for Your Baby and Young Child: Birth to Age 5, 6th Edition. [updated 2019 Jan 1, accessed 2019 Jun 19].

Amrhein V, Greenland S, McShane B. 2019. Retire statistical significance. Nature 567:305-307.

Anderson EL, Sheehan PJ, Kalmes RM, Griffin JR. 2017. Assessment of health risk from historical use of cosmetic talcum powder. Risk Anal. 37(5):918-928.

Arellano-Orden E, Romero-Falcon A, Juan JM, Jurado MO, Rodriguez-Panadero F, Motes-Worboys A. 2013. Small particle-size talc is associated with poor outcome and increased inflammation in thoracoscopic pleurodesis. Respiration 86:201-209.

Aylott RI, Byrne GA, Middleton JD, Roberts. 1979. Normal use levels of respirable cosmetic talc: preliminary study. Int J Cosmet Sci. 1(3):177-186.

Ballman K. 2019. Expert Report of Karla Ballman, PhD for general causation Daubert hearing. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Berge W, Mundt K, Luu H, Boffetta P. 2018. Genital use of talc and risk of ovarian cancer: a meta-analysis. Eur J Cancer Prev. 27(3):248-257.

Bevan RJ, Kreiline R, Levy LS, Warheit DB. 2018. Toxicity testing of poorly soluble particles, lung overload and lung cancer. Regul Toxicol Pharmacol. 100: 80-91.

Booth M, Beral V, Smith P. 1989. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 60(4):592-598.

Bricker OP, Nesbitt HW, Gunter WD. 1973. The stability of talc. American Mineralogist 58:64-72.

Burns AM, Barlow CA, Banducci AM, Unice KM, Sahmel J. 2019. Potential Airborne Asbestos Exposure and Risk Associated with the Historical Use of Cosmetic Talcum Powder Products. Risk Anal. 39(10):2272-2294.

Buz'Zard AR and Lau BHS. 2007. Pycnogenol® reduces talc-induced neoplastic transformation in human ovarian cell cultures. Phytotherapy Research 21:579-586.

Campion A, Smith KJ, Fedulov AV, Gregory DZ, Fan Y, Godleski JJ. 2018. Identification of foreign particles in human tissues using raman microscopy. Anal. Chem. 90:8362-8369.

Canada. [1978]. *Food and Drug Regulations*. C.R.C., c.870.

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C. 1999, c.33. Canada Gazette Part III, vol. 22, no. 3.

Carr CJ. 1995. Talc: Consumer Uses and Health Perspectives. Proceedings of a workshop. Bethesda, Maryland, January 31–February 1, 1994. Regul Toxicol Pharmacol. 21(2):211-215.

Carson A. 2018. Rule 26 Expert Report of Arch Carson, MD, PHD. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Celentano DD. Szklo M. 2019. Gordis Epidemiology. 6th Ed. Elsevier. p 193-196.

Chaffin CL, VandeVoort CA. 2013. Follicle growth, ovulation and luteal formation in primates and rodents: a comparative perspective. Experimental Biology and Medicine 238:539-548.

Chang S, Risch HA. 1997. Perineal talc exposure and risk of ovarian carcinoma. Cancer. 79(12):2396-2401.

Chang CJ, Tu YK, Chen PC, and Yang HY. 2017. Occupational exposure to talc increases the risk of lung cancer: A meta-analysis of occupational cohort studies. Can Respir J. 2017:1-12.

ChemIDplus [database]. 1993-. Bethesda (MD): U.S. National Library of Medicine. [updated 2017 April 11; accessed 2017 May 26].

Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. 1992. Risk factors for epithelial ovarian cancer in Beijing, China. Int J Epidemiol. 21(1):23-29.

Cheng DS, Rogers J, Wheeler A, Parker R, Teixeira L, Light RW. 2000. The effects of intrapleural polyclonal anti-tumor necrosis factor alpha (TNF alpha) Fab fragments on pleurodesis in rabbits. Lung. 178(1):19–29.

[CIMT] Canadian International Merchandise Trade Database [database]. 2017. Ottawa (ON): Government of Canada. [accessed 2017 October].

[CIR] Cosmetic Ingredient Review Expert Panel. 2013. Safety Assessment of Talc as Used in Cosmetics. Final Report [PDF]. Washington (DC): Cosmetic Ingredient Review. [accessed 2017 November].

Cogliano VJ, Baan RA, Straif K, Grosse Y, Secretan MB, Ghissassi FE, Kleihues P. 2004. The science and practice of carcinogen identification and evaluation. Environ Health Perspect. 112(13):1269-1274.

Cook LS, Kamb ML, Weiss NS. 1997. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol. 145(5):459-465.

[CPCat] Chemical and Product Categories [database]. 2014. Ver. 04. Washington (D.C.): U.S. Environmental Protection Agency. [updated 2014 May 21; accessed 2014 Nov 21]. [Database described in Dionisio KL, Frame AM, Goldsmith MR, Wambaugh JF, Liddell A, Cathey T, Smith D, Vail J, Ernstoff AS, Fantke P, et al. 2015. Exploring consumer exposure pathways and patterns of use for chemicals in the environment. Toxicol Rep. (2):228-237.].

[CPID] Consumer Product Information Database [database]. 2017. McLean (VA): DeLima Associates. [accessed 2017 Nov 21].

Cramer DW, Welch WR, Scully RE, Wojciechowski CA. 1982. Ovarian cancer and talc: a case-control study. Cancer. 50(2):372-376.

Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, Finn OJ. 2005. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 14(5):1125-1131.

Cramer DW, Welch WR, Berkowitz RS and Godleski JJ. 2007. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long term genital exposure to cosmetic talc. Obstet Gynecol. 110(2 Pt 2):498-501.

Cramer DW. 2012. The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin North Am. 26:1:1-12.

Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. 2016. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. Epidemiology. 27(3):334-346.

Cruthirds TP, Cole FH, Paul RN. 1977. Pulmonary talcosis as a result of massive aspiration of baby powder. South Med J. 70(5):626-628.

[CTFA] Cosmetic, Toiletry and Fragrance Association. 1983. Summary for the Results of Surveys of the amount and Frequency of use of cosmetic products by Women. Report Prepared by Pitkin B, Rodericks JV, Turnbull D. Washington (DC): CTFA Inc.

[CTFPHC] Canadian Task Force on Preventive Health Care. 2020. Screening for Ovarian Cancer: U.S. Preventive Services Task Force Reaffirmation Recommendation Statement. [accessed 2020 August].

[Danish EPA] Danish Environmental Protection Agency. 2016. Evaluation of health hazards by exposure to talcum, cosmetic grade (non-fibrous) and proposal of a health-based quality criterion for ambient air [PDF]. Denmark: Danish Environmental Protection Agency. ISBN: 978-87-93529-23-6.

De Boer CH. 1972. Transport of particulate matter through the human female genital tract. J Reprod Fertil. 28(2):295-297.

Dement JM, Mangin JH, Wallingfor KM, Shuler PJ, Sumwalde RD. 1972. Fiber Exposure During Use of Baby Powders. Preliminary Report. Cincinnati (OH): Environmental Investigations Branch, National Institute for Occupational Safety and Health.

Deng J, Wang L, Chen H, Li L, Ma Y, Ni J, Li Y. 2013. The role of tumour-associated MUC1 in epithelial ovarian cancer metastasis and progression. Cancer metastasis reviews. 32(3-4):535-51

Diette G. 2019. Expert Report of Gregory Diette, MD, MHS. For general causation Daubert hearing. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Douglas A, Karov J, Daka J, Hinberg I. 1998. Detection and Quantitation of Talc on Latex Condoms. Contraception. 58(3):153-155.

[DPD] Drug Product Database [database]. [modified 2018 June 12]. Ottawa (ON): Government of Canada. [accessed 2018 Aug 15].

[EC] Environment Canada. 2013. DSL Inventory Update data collected under the *Canadian Environmental Protection Act, 1999*, section 71: *Notice with respect to certain substances on the Domestic Substances List.* Data prepared by: Environment Canada, Health Canada; Existing Substances Program.

[ECCC] Environment and Climate Change Canada. 2018. Science approach document: ecological risk classification of inorganic substances. Ottawa (ON): Government of Canada.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. 2017. Targeted information gathering for screening assessments under the Chemicals Management Plan (February to July 2017). Data prepared by: ECCC, Health Canada; Existing Substances Program.

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2017 Mar 12]. Categorization of chemical substances. Ottawa (ON): Government of Canada. [accessed 2018 Aug 30].

Edelstam GAB, Sjösten ACE, Ellis, H. 1997. Retrograde migration of starch in the genital tract of rabbits. Inflammation. 21(5):489-499.

Egli GE, Newton M. 1961. The transport of carbon particles in the human female reproductive tract. Fertil Steril. 12:151-155.

[EU] Commission of the European Communities. [modified 2001 Oct 1]. Report from the Commission on Dietary Food Additive Intake in the European Union. Brussels (BE): Commission of the European Communities.

[EuroTalc] Scientific Association of European Talc Producers. 2017. "What is talc?" Brussels (BE): EuroTalc. [accessed 2017 May 29]

[FAO] Food and Agriculture Organization of the United Nations. 2006. Combined Compendium of Food Additives Specifications: Sixty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives. FAO Food and Nutrition Paper 52.

[FCC] Food Chemicals Codex, Tenth edition. 2016. Rockville (MD): The United States Pharmacopeial Convention.

Fedak KM, Bernal A. Capshaw ZA, Gross S. 2015. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 12:14.

Feigin DS.1986.Talc: understanding its manifestations in the chest. Am J Roentgenol. 146(2):295-301.

Ficheux AS, Wesolek N, Chevillotte G, Roudot AC. 2015. Consumption of cosmetic products by the French population. First part: Frequency data. Food Chem Toxicol. 78:159-169.

Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, Murphy J, Ghadirian P, Friedman E, Foulkes WD, Kim-Sing C, Wagner T, Tung N, Couch F, Stoppa-Lyonnet D, Ainsworth P, Daly M, Pasini B, Gershoni-Baruch R, Eng C, Olopade OI, McLennan J, Karlan B, Weitzel J, Sun P, Narod SA. 2006. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. 296:185-192.

Fine LJ, Peters JM, Burgess WA, DiBerardinis LJ. 1976. Studies of respiratory morbidity in rubber workers – IV. Respiratory morbidity in talc workers. Arch Environ Health 31: 195– 200.

Fiume MM, Boyer I, Bergfeld WG, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks Jr JG, Shank RC, Slaga TH, Snyder PW, Anderson FA. 2015. Safety Assessment of Talc Used in Cosmetics. Int J Toxicol. 34(1 suppl):66S-129S.

Fletcher NM, Harper AK, Memaj I, Fan R, Morris RT, Saed GM. 2019. Molecular basis supporting the association of talcum powder used with increased risk of ovarian cancer. Reproductive Sciences. DOI: 10.1177/1933719119831773.

Franco EL, Correa P, Santella RM, Wu X, Goodman SN, Petersen GM. 2004. Role and limitations of epidemiology in establishing a causal association. Seminars in Cancer Biology 14:413-426.

Frank C, Jorge L. 2011. An uncommon hazard: Pulmonary talcosis as a result of recurrent aspiration of baby powder. Respir Med CME. 4(3):109-111.

Frosch PJ, Kligman AM. 1976. The chamber-scarification test for irritancy. Contact Derm. 2:314-324.

Gabriel IM, Vitonis AF, Welch WR, Titus L, Cramer DW. 2019. Douching talc use, and risk for ovarian cancer and conditions related to genital tract inflammation [PDF]. DOI: 10.1158/1055-9965.EPI-19-0375

Gates MA, Tworoger SS, Terry KL, Titus-Ernstoff L, Rosner B, De Vivo I, Cramer DW, Hankinson SE. 2008. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 17(9):2436-2444.

Gates MA, Rosner BA, Hecht JL, Tworoger SS. 2010. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 171(1):45-53.

Gendler SJ, Spicer AP. 1995. Epithelial mucin genes. Annu Rev Physiol. 57:607-634.

Genofre EH, Marchi E, Vargas FS. 2007. Inflammation and clinical repercussions of pleurodesis induced by intrapleural talc administration. Clinics 62:5

Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, Hankinson SE. 2000. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst. 92(3):249-252.

Gibbs AE, Pooley FD, Griffiths DM, Mitha R, Craighead JE, Ruttner JR. 1992. Talc pneumoconiosis: a pathologic and mineralogic study. Hum Pathol. 23(12):1344-1354.

Gibel W, Lohs K, Horn KH, Wildner GP, Hoffmann F. 1976. Experimental study on cancerogenic activity of asbestos filters. Arch Geschwulstforsch. 46:437-442.

Godard B, Foulkes WD, Provencher D, Brunet JS, Tonin PN, Mes-Masson AM, Narod SA, Ghadirian P. 1998. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. Am J Obstet Gynecol. 179(2):403-410.

Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. 2016. Douching, talc use, and risk of ovarian cancer. Epidemiology. 27(6):797-802.

Goodman MT, Lurie G, Thompson PJ, McDuffie KE, Carney ME. 2008. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. Endocr Relat Cancer. 15:1055-1060.

Goodman JE, Kerper LE, Prueitt RL, Marsh CM. 2020. A critical review of talc and ovarian cancer, Journal of Toxicology and Environmental Health, Part B, DOI: 10.1080/10937404.2020.1755402

Gould SR, and Barnardo DE. 1972. Respiratory distress after talc inhalation. Brit J Dis Chest. 66:230-233.

Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, Ward B. 1997. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. Int Cancer. 71(6):948-951.

Grimes DA Schultz KF. 2002. Bias and causal associations in observational research. The Lancet 359: 248-252.

Gysbrechts C, Michiels E, Verbeken E, Verschakelen J, Dinsdale D, Nemery B, Demedts M. 1998. Interstitial lung disease more than 40 years after a 5 year occupational exposure to talc. Eur Respir J. 11(6):1412-1415.

Hamilton TC, Fox H, Buckley CH, Henderson WJ, Griffiths K. 1984. Effects of talc on the rat ovary. Br J Exp Pathol. 65(1):101-106.

Harlow BL, Weiss NS. 1989. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am J Epidemiol. 130(2):390-394.

Harlow BL, Cramer DW, Bell DA, Welch WR. 1992. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol. 80(1):19-26.

Hartge P, Hoover R, Lesher LP, McGowan L. 1983. Talc and ovarian cancer. J Am Med Assoc. 250(14):1844.

Health Canada. 2010. PMRA list of formulants [PDF]. Ottawa (ON): Government of Canada.

Health Canada. 2015. Natural Health Products monograph for Traditional Chinese Medicine Ingredients (TCMI). Ottawa (ON): Government of Canada.

Health Canada. 2018. Diaper rash products  monograph [PDF]. Ottawa (ON): Government of Canada.

Health Canada. 2020. Personal Care Products Workbook. Recommended Defaults. Last updated: October 19, 2020. Internal Draft. Unpublished report. Ottawa (ON): Existing Substances Risk Assessment Bureau, Health Canada.

Health Canada. [modified 2017 Jun 15]. Application of weight of evidence and precaution in risk assessment. Ottawa (ON): Government of Canada. [accessed 2019 Mar 11].

Health Canada. [modified 2018 Jun 14]. Cosmetic ingredient hotlist: list of ingredients that are prohibited for use in cosmetic products. Ottawa (ON): Government of Canada. [accessed 2018 Aug 30].

Health Canada. [modified 2020 April 9]. 8. List of permitted food additives with other accepted uses (lists of permitted food additives). Ottawa (ON): Government of Canada. [accessed 2020 Oct 26].

Heller DS, Westhoff C, Gordon RE, Katz N. 1996. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am J Obstet Gynecol. 174(5):1507-1510.

Henderson WJ, Joslin CAF, Griffiths K, Turnbull AC. 1971. Talc and carcinoma of the ovary and cervix. BJOG: Int J Obstet Gynaecol. 78(3):266-272.

Henderson WJ, Hamilton TC, Griffiths K. 1979. Talc in normal and malignant ovarian tissue. The Lancet March 3, 1979 p499.

Henderson WJ, Hamilton TC, Baylis MS, Pierrepoint CG, Griffiths K. 1986. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ Res. 40(2):247-250.

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. 2003. Measuring inconsistency in meta-analyses.BMJ 327:557-560.

Hill AB. 1965. The environment and disease: association or causation? Proc R Soc Med. 58:295-300.

Hollinger MA. 1990. Pulmonary toxicity of inhaled and intravenous talc. Toxicol Lett. 52(2):121-127; discussion 117-119.

Houghton SC, Reeves KW, Hankinson SE, Crawford L, Lane D, Wactawski-Wende J, Thomson CA, Ockene JK, Sturgeon SR. 2014. Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst. 106(9).

Household Products Database [database]. 1993-. Bethesda (MD): National Library of Medicine (US). [updated 2016 September; accessed 2017 June 19].

[HSDB] Hazardous Substances Data Bank [database]. 2005. CAS RN 14807-96-6. Bethesda (MD): National Library of Medicine (US). [complete update 2005 May 2; accessed 2017 Nov 21].

Huncharek M, Geschwind JF, Kupelnick B. 2003. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Research 23(2C):1955-1960.

Huncharek M, Muscat J. 2011. Perineal talc use and ovarian cancer risk: a case study of scientific standards in environmental epidemiology. European Journalof Cancer Prevention 20:6:501-507.

[IARC] International Agency for Research on Cancer. 1987. Talc not containing asbestiform fibres (group 3). Talc containing asbestiform fibres (group 1). Summaries & Evaluations. Suppl 7:349.

[IARC] International Agency for Research on Cancer. 2010. Carbon Black, Titanium Dioxide, and Talc, IARC Monogr Eval Carcinog Risks Hum. 93:277-413.

[JECFA] Joint FAO/WHO Expert Committee on Food Additives. 2006. Compendium of Food Additive Specifications. FAO JECFA Monograph 1.

Johnson & Johnson Consumer Health. 2020. “Facts about talc”. [accessed 2020 August]

Johnson & Johnson Consumer Inc. 2020. Johnson's® Baby Talcum Powder: A Comprehensive Review. Unpublished report submitted to Health Canada under the Chemicals Management Plan initiative. Ontario (ON): Health Canada. [restricted access]

Johnson KE, Popratiloff A, Fan Y, McDonald S, Godleski JJ. 2020. Analytic comparison of talc in commercially available baby powder and in pelvic tissues resected from ovarian carcinoma patients.Gynecologic Oncology. 159(2):527-553.

Kane SE. 2018. Rule 26 Expert Report of Sarah E. Kane, MD. United States District Court District of New Jersey. MDL No. 16-2738 (FLW). [accessed 2020 July].

Keskin N, Teksen YA, Ongun EG, Ozay Y, Saygili H. 2009. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Arch Gynecol. 280(6):925-931.

Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, Callahan MJ, Garner EO, Gordon RW, Birch C, Berkowitz RS, Muto MG, Crum CP. 2007. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol. 31(2):161-169.

Kissler S, Siebzehnruebl E, Kohl J, Mueller A, Hamscho M, Gaetje R, Ahr A, Rody A, Kaufman N. 2004. Uterine contractility and directed sperm transport assessed by hysterosalpingoscintigraphy (HSSG) and intrauterine pressure (IUP) measurement. Acta Obstet Gynecol Scand 83:369-374.

Kogel JE, Trivedi NC, Barker JM, Krukowski ST, eds. 2006. Industrial Minerals and Rocks. 7th ed. Littleton (CO): Society for Mining, Metallurgy, and Exploration, Inc.

Kuhn E, Kurman RJ, Shih I-M. 2012. Ovarian cancer is an imported disease: fact or fiction? Curr Obsstet Gynecol Rep 1:1:1-9.

Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G. 1996. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. Human Reproduction. 11:3:627-632.

Kurta ML, Moysich KB, Weissfeld JL, Youk AO, Bunker CH, Edwards RP, Modugno F, Ness RB, Diergaarde B. 2012. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. Cancer Epidemiol Biomarkers Prev. 21(8):1282-1292.

Kurman RJ, Shih I-M. 2011. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Hum. Pathol. 42(7):918-931.

Kurman RJ, Shih I-M. 2016. The Dualistic Model of Ovarian Carcinogenesis. Revisited, Revised and Expanded. Am. J. Pathol. 186(4):733-747.

Langseth H, Kjærheim K. 2004. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. Scand J Work Environ Health. 30(5):356-361.

Langseth H, Hankinson SE, Siemiatycki J, Weiderpasse E. 2008. Perineal use of talc and risk of ovarian cancer. J Epidemiol Community Health. 62(4):358-360.

Li M, Zhou T-H, Gao Y, Zhang N, Li J-C. 2007. Ultrastructure and estrogen regulation of the lymphatic stomata of ovarian bursa in mice. The Anatomical Record 290:1195-1202.

Leikauf, GD. 2013. Toxic responses of the respiratory system. in Casarett and Doull's Toxicology: The Basic Science of Poisons (Eighth Edition). (Ed: Klaassen, CD), McGraw-Hill Education, New York, NY, p 691-732..

[LNHPD] Licensed Natural Health Products Database [database]. [modified 2018 Feb 6]. Ottawa (ON): Government of Canada. [accessed 2018 Aug 14].

Lo-Ciganic WH, Zgibor JC, Bunker CH, Moysich KB, Edwards RP, Ness RB. 2012. Aspirin, non-aspirin non-steroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. Epidemiol 23:311-319.

Lundberg M, Wrangsjo K, Johansson SGO. 1997. Latex allergy from glove powder – an unintended risk with the switch from talc to cornstarch. Allergy 52:1222-1228.

[MAC] Mining Association of Canada. 2019. Facts and Figures 2019. The state of Canada's mining industry [PDF]. [accessed 2020 Nov 19].

[MAK-Commission] The MAK-Collection for Occupational Health and Safety. 2012. Talc (without asbestos fibres) (respirable fraction). Weinheim (DE): Wiley-VCH Verlag GmbH & Co. KGaA. The MAK-collection Part I: MAK Value Documentations, Vol. 22. 226-279.

Mandarino A, Gregory DJ, McGuire CC, Leblanc BW, Will H, Mejias Rivera L, Godleski JJ, Fedulov AV. 2020. The effect of talc particles on phagocytes in co-culture with ovarian cancer cells. Environmental Research 180:1-12.

Marchiori E, Lourenço S, Gasparetto TD, Zanetti G, Mano CM, Nobre LF. 2010. Pulmonary talcosis: imaging findings. Lung. 188(2):165-171.

McDonald SA, Fan Y, Welch WR, Cramer DW, Godleski JJ. 2019a. Migration of talc from the perineum to multiple pelvic organ sites. Five case studies with correlative light and scanning electron microscopy. Am J Clin Pathol. 152(5):590-607.

McDonald SA, Fan Y, Welch WR, Cramer DW, Stearns RC, Sheedy L, Katler M, Godleski JJ. 2019b. Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes. Ultrastructural Pathology 43:1:13-27.

McTiernan A. 2019. Report of Anne McTiernan, MD, PHD, to the house of representatives subcommittee on the economic and consumer policy. March 12, 2019. [accessed 2020 April]

Merlo C. 2019. Expert Report of Christian Merlo, MD, MPH. For general causation Daubert hearing. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Merritt MA, Nagle CM, Webb PM, Bowtell D, Chenevix-Trench G, Green A, DeFazio A, Gertig D, Traficante N, Moore S, et al. 2008. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int J Cancer. 122(1):170-176.

Mills PK, Riordan DG, Cress RD, Young HA. 2004. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. Int J Cancer. 112(3):458-464.

Moore N. 2019. Rule 26 Report of H. Nadia Moore, PHD, DABT, ERT. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM. 2009. Ovarian cancer risk factors in African-American and white women. Am J Epidemiol. 170(5):598-606.

Moorman PG. 2018. Rule 26 Expert Report of Patricia G. Moorman, MSPH, PHD. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Morrison JC, Blanco LZ, Vang R, Ronnett BM. 2015. Incidental serous tubal intraepithelial carcinoma and early invasive serous carcinoma in the nonprophylactic setting: analysis of a case series. Am J Surg Pathol. 39(4):442-453.

Muscat J, Huncharek M, Cramer DW. 2005. Talc and anti-MUC1 antibodies. Cancer Epidemiol Biomarkers Prev. 14(11 Pt. 1):2679.

Muscat JE, Huncharek, MS. 2008. Perineal talc use and ovarian cancer: a critical review. Eur J Cancer Prev. 17(2):139-146.

Narod SA. 2016. Talc and ovarian cancer. Gynecol Oncol. 141:410-412.

[NASEM] National Academy of Sciences, Engineering, and Medicine. 2016. Ovarian cancers: evolving paradigms in research and care. Washington (D.C.): National Academy Press.

[NCI] National Cancer Institute. Ovarian, fallopian tube, and primary peritoneal cancer prevention (PDQ®) – health professional version. [accessed 2019 September].

[NCI-SEER] National Cancer Institute – Surveillance, Epidemiology and End Results Program. Cancer Stat Facts: Ovarian Cancer. [accessed 2020 July].

Neel BG. 2019. Expert Report of Benjamin G. Neel, MD, PHd. For general causation Daubert hearing. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ. 2000. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 11(2):111-117.

[NHPID] Natural Health Products Ingredients Database [database]. [modified 2019 Sep 26]. Ottawa (ON): Government of Canada. [accessed 2018 Aug 14].

[NHS] Nurses' Health Study. 2020. [accessed 2020 August].

[NIOSH] National Institute for Occupational Safety and Health (US). 2014. Talc (silica and fibre free). International Chemical Safety Card (ICSC). Atlanta (GA): Centre for Disease Control. ICSC # 0329. [accessed 2018 Mar].

Nishida T, Sugiyama T, Kataoka A, Ushijima K, Yakushiji. 1998. Histologic characterization of rat ovarian carcinoma induced by intraovarian insertion of a 7,12-dimethylbenz[a]anthracene-coated suture. Cancer. 83(5):965-970.

[NPRI] National Pollutant Release Inventory. 2018. NPRI Datasets: Substance: PM10 - Particulate Matter <= 10 Microns, Company/Facility information: Imerys Talc Canada Inc. (2017). Ottawa (ON): Government of Canada. Search results for $PM_{10}$ at Imerys Talc Canada Inc. [updated 2018 June 14].

[NTP] National Toxicology Program. 1993. NTP technical report on the toxicology and carcinogenesis studies of talc (CAS NO. 14807-96-6) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park (NC): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. National Toxicology Program, NTP TR 421, NIH Publication No. 93-3152.

[NVWA] Netherlands Food and Consumer Product Safety Authority. 2018. Asbestos in cosmetic products: Study of asbestos in talc-containing cosmetic products [PDF]. Utrecht (NL): Government of the Netherlands. [accessed 2019 Oct 23].

Oberdorster G. 1995. The NTP talc inhalation study: a critical appraisal focussed on lung particle overload. Regul Toxicol Pharmacol. 21(2):233-241.

O'Brien KM, Tworoger SS, Harris HR, Anderson GL, Weinberg CR, Trabert B, Kaunitz AM, D'Aloisio AA, Sandler DP, Wentzensen N. 2020. Association of powder use in the genital area with risk of ovarian cancer. Journal of the American Medical Association 323(1):49-59.

[OECD] Organisation for Economic Co-operation and Development Screening Information Dataset (SIDS). 2004. Synthetic Amorphous Silica and Silicates. SIDS Initial Assessment Report for SIAM 19 [PDF]. Berlin (DE): UNEP Publications. [accessed 2018 Sept].

[OSHA] Occupational Safety and Health Administration. 1999. Talc (not containing asbestos). Chemical Sampling Information. Washington (DC): Occupational Safety and Health Administration (US). [accessed 2017 Nov 7].

Patarino F, Norbedo S, Barbi E, Poli F, Furlan S, Savron F. 2010. Acute Respiratory Failure in a Child after Talc Inhalation. Respiration. 79:340.

Penninkilampi R, Eslick GD. 2018. Perineal talc use and ovarian cancer: A systemic review and meta-analysis. Epidemiology. 29(1):41-49.

Peters A, Veronesi B, Calderón-Garcidueñas L, Gehr P, Chen LC, Geiser M, Reed W, Rothen-Rutishauser, Schürch S, Schulz H. 2006. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol. 3:13.

Phillips JC, Young PJ, Hardy K, Gangolli SC.1978. Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit. Food Cosmet Toxicol.16(2):161-163.

Pickrell JA, Snipes MB, Benson JM, Hanson RL, Jones RK, Carpenter RL, Thompson JJ, Hobbs CH, Brown SC. 1989. Talc deposition and effects after 20 days of repeated inhalation exposure of rats and mice to talc. Environ Res. 49:233-245.

Piek JM, van Diest PJ, Zweemer RP, Jansen JW, Poort-Keesom RJ, Menko FH, Gille JJ, Jongsma AP, Pals G, Kenemans P, Verheijen RH. 2001. Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. J Pathol. 195(4):451-456.

Piek JMJ, Verheijen RHM, Kenemans P, Massuger LF, Bulten H, van Diest PJ. 2003. BRCA1/2-related ovarian cancers are of tubal origin: a hypothesis. Gynecol Oncol. 90(2):491.

Pinheiro SP, Hankinson SE, Tworoger SS, Rosner BA, McKolanis JR, Finn OJ, Cramer DW. 2010. Anti-MUC1 antibodies and ovarian cancer risk: prospective data from the Nurses' Health Studies. Cancer Epidemiol Biiomarkers Prev 19:6:1595-1601.

Pooley, FD. 1972. Report of dusting experiment performed with Johnson and Johnson baby powder. UK: University College, Cardiff, UK. Unpublished report.

Przybycin CG, Kurman RJ, Ronnett BM, Shih I-M, Vang R. 2010. Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol. 34(1):1407-1416.

Purdie D, Green A, Bain C, Siskand V, Ward B, Hacker N, Quinn M, Wright G, Russell P, Susil B. 1995. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Int J Cancer. 62:678-684.

Purdie DM, Bain CJ, Siskind V, Webb PM, Green AC. 2003. Ovulation and risk of epithelial ovarian cancer. International journal of cancer Journal international du cancer. 104:2:228-32.

Ramelet AA. 1991. A rare complication of ambulatory phlebectomy. Talc Granuloma (French). Phlébologie 44:865-871.

Rasmussen CB, Kjaer SK, Albieri V, Bandera EV, Doherty JA, Høgdall E, Webb PM, Jordan SJ, Rossing MA, Wicklund KG, et al.; on behalf of the Ovarian Cancer Association Consortium. 2017. Pelvic inflammatory disease and the risk of ovarian cancer and borderline ovarian tumors: a pooled analysis of 13 case-control studies. Am J Epidemiol. 185(1):8-20.

Rasmussen P, Levesque C, Niu J, Gardner HD, Nilsson G, Macey K. 2019. Characterization of airborne particles emitted during application of cosmetic talc products. Int. J. Environ. Res. Public Health. 16(20): 3830.

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. 2006. Cosmetics fact sheet: to assess the risks for the consumer: updated version for ConsExpo 4 [PDF]. Bilthoven (NL): RIVM. Report No.: 320104001/2006. [accessed 2020 Oct 29].

Rosenblatt KA, Szklo M, Rosenshein NB. 1992. Mineral fiber exposure and the development of ovarian cancer. Gynecol Oncol. 45(1):20-25.

Rosenblatt KA, Weiss NS, Cushing-Haugen KL, Wicklund KG, Rossing MA. 2011. Genital powder exposure and the risk of epithelial ovarian cancer. Cancer Causes Control. 22(5):737-742.

Russell RS, Merz RD, Sherman WT, Sivertson JN. 1979. The determination of respirable particles in talcum powder. Food Cosmet Toxicol. 17(2):117-122.

Sato E, McDonald SA, Fan Y, Peterson S, Brain JD and Godleski JJ. 2020. Analysis of particles from hamster lungs following pulmonary talc exposures: implications for pathogenicity. Part Fibre Toxicol. 17(20):1-16.

Schildkraut JM, Abbott SE, Alberg AJ, Bandera EV, Barnholtz-Sloan JS, Bondy ML, Cote ML, Funkhouser E, Peres LC, Peters ES, et al. 2016. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). Cancer Epidemiol Biomarkers Prev. 25(10):1411-1417.

SDS Search Tool [database]. 2016. Ottawa (ON): Government of Canada. [updated 2016 Sept 15; accessed 2017 Nov 22]. [restricted access].

Seidman JD, Cho KR, Ronnett BM, Kurman RJ. 2011. Surface epithelial tumors of the ovary. In: Kurman, RJ.; Ellenson, LH.; Ronnett, BM., editors. Blaustein's Pathology of the Female Genital Tract. New York: Springer Verlag; pp. 679-784.

Shakoor A, Rahatullah A, Shah AA, Zubairi ABS. 2011. Pulmonary talcosis 10 years after brief teenage exposure to cosmetic talcum powder. BMJ Publishing Group. BMJ Case Reports. 2011:bcr0820114597.

Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker JG. 1996. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. Fertil Steril. 65:13-18.

Siemiatycki J. 2018. Rule 26 Expert Report of Jack Siemiatycki, MSc, PhD. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Simsek F, Turkeri L, Ilker Y, Kullu S, Akdas A. 1992. Severe obstruction of the urinary tract due to talcum powder granuloma after surgery. A case report. Int Urol Nephrol. 24:31-34.

Singh S. 2018. Rule 26 Expert Report of Sonal Singh, MD, MPH. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Sister Study 2020. The Sister Study. [accessed 2020 August].

Sjosten ACE, Ellis H, Edelstam GAB. 2004. Retrograde migration of glove powder in the human female genital tract. Human Reproduction 19:4:991-995.

Smith EB. 2018. Rule 26 Expert Report of Ellen Blair Smith, MD. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Smith-Bindman R. 2018. Rule 26 Expert Report of Rebecca Smith-Bindman, MD. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Statistics Canada. 2016. Data Tables, 2016 Census. Census family structure including stepfamily status (9) and number and age combinations of children (29) for census families with children in private households of Canada, Provinces and Territories, census metropolitan areas and census agglomerations, 2016 and 2100 censuses – 100% data. Ottawa (ON): Government of Canada. [accessed 2017 Nov 23].

Steiling W, Almeida JF, Assaf Vandecasteele H, Gilpin S, Kawamoto T, O'Keeffe L, Pappa G, Rettinger K, Rothe H, Bowden AM. 2018. Principles for the safety evaluation of cosmetic powders. Toxicol Lett. 297:8-18.

Taher MK, Farhat N, Karyakina N, Shilnikova N, Ramoju S, Gravel CA, Krishnan K, Mattison D, Wen S-Wu, Krewski D. 2019. Critical review of the association between perineal use of talc powder and risk of ovarian cancer. Reproductive Toxicology. DOI: https://doi.org/10.1016/j.reprotox.2019.08.015.

Terry KL, Karageorgi S, Shvetsov YB, Merritt MA, Lurie G, Thompson PJ, Carney ME, Weber RP, Akushevich L, Lo-Ciganic WH, et al. 2013. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. Cancer Prev Res. 6(8):811-821.

Trabert B, Pinto L, Hartge P, Kemp T, Black A, Sherman ME, Brinton LA, Pfeiffer RM, Shields MS, Chaturvedi AK, Hildesheim A, and Wentzensen N. 2014. Pre-diagnostic serum levels if inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. Gynecol Oncol. 135(2):297-304.

Trabert B. 2016. Body powder and ovarian cancer risk – what is the role of recall bias? Cancer Epidemiol Biomarkers Prev. 25:10:1369-1370.

Tran TH, Steffen JE, Clancy KM, Bird T, Egilman DS. 2019. Talc asbestos, and epidemiology: Corporate influence and scientific incognizance. Epidemiology. 30(6): 783-788.

Tukiainen P, Nickels J, Taskinen E, Nyberg M. 1984. Pulmonary granulomatous reaction: talc pneumoconiosis or chronic sarcoidosis? Bri J Ind Med. 41:84-87.

Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. 1993. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer. 55(3):408-410.

United States. 2016. Federal Register. Banned Devices; Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove, A Rule by the Food and Drug Administration on 12/19/2016. US: Federal Register (US). Vol. 81, No. 243. 21 CFR 878. p. 91722-91731 [accessed 2018 Jan 3].

[U.S. EPA] United States Environmental Protection Agency. 1992. Health Assessment Document for Talc. Washington (D.C.): Office of Research and Development. Report No. EPA 600/8-91/217.

[U.S. EPA] United States Environmental Protection Agency. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Research Triangle Park (NC): U.S. EPA, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development.

[U.S. EPA] United States Environmental Protection Agency. 2005. Guidelines for Carcinogen Risk Assessment [PDF]. Washington (D.C.): U.S. EPA, EPA/630/P-03/001F.

[U.S. EPA] United States Environmental Protection Agency. 2009. Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part F, Supplemental Guidance for Inhalation Risk Assessment). Washington (D.C.): U.S. EPA, Office of Superfund Remediation and Technology Innovation.

[U.S. EPA] United States Environmental Protection Agency. 2011. Exposure Factors Handbook 2011 Edition (Final Report). Washington (D.C.): U.S. EPA, EPA/600/R-09/052F.

[U.S. FDA] United States Food and Drug Administration. 2014. Letter to S Epstein re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP [PDF]. Department of Health and Human Services.

[U.S. FDA] United States Food and Drug Administration. 2019a Code of Federal Regulations Title 21, Volume 3: Section 182.70 Substances migrating from cotton and cotton fabrics used in dry food packaging. [revised as of 2019 Apr 1] Silver Spring (MD): U.S. Food and Drug Administration. [accessed 2020 Oct 28].

[U.S. FDA] United States Food and Drug Administration. 2019b Code of Federal Regulations Title 21, Volume 3: Section 182.90 Substances migrating to food from paper and paperboard products. [revised as of 2019 Apr 1]. Silver Spring (MD): U.S. Food and Drug Administration. [accessed 2020 Oct 28].

[U.S. FDA] United States Food and Drug Administration. 2020a. Executive Summary: Preliminary Recommendation on Testing Methods for Asbestos in Talc and Consumer Products Containing Talc [PDF]. January 6, 2020. Silver Spring (MD): U.S. Food and Drug Administration. [accessed 2020 Sept 29].

[U.S. FDA] United States Food and Drug Administration. 2020b. Talc. Silver Spring (MD): U.S. Food and Drug Administration. [accessed 2020 Sept 29].

[USGS] United States Geological Survey. 2000. U.S. Talc-Baby Powder and Much More [PDF]. Reston (VA): U.S. Geological Survey. USGS Fact Sheet FS-065-00. [accessed 2017 May 29].

[USGS] United States Geological Survey. 2020. Mineral Commodity Summaries. Talc and Pyrophyllite [PDF]. Reston (VA): U.S. Geological Survey. [accessed 2020 Oct 23].

[USP] United States Pharmacopeia. 2011. USP Monographs: Talc. Talc Revision Bulletin Official August 1, 2011 [PDF]. (US): The United States Pharmacopeial Convention. [accessed 2018 May 3].

[USP] United States Pharmacopeia. 2019. FAQs: Modernization of the USP Talc Monograph. (US): The United States Pharmacopeial Convention. [accessed 2019 Oct 23].

[USP] US Pharmacopeia. 2020a. USP-NF Talc Notice of Intent to Revise. (US): The United States Pharmacopeial Convention. [accessed 2020 Sept 9].

[USP] US Pharmacopeia. 2020b. Modernization of Asbestos Testing in USP-Talc – Part 2. (US): The United States Pharmacopeial Convention. [accessed 2020 Sept 30] [restricted access].

Vallyathan NV, Craighead JE.1981. Pulmonary pathology in workers exposed to nonasbestiform talc. Hum Pathol.12(1):28-35.

van den Heuvel NM,. Smit HJ, Barbierato SB, Havenith CE, Beelen RH, Postmus PE. 1998. Talc-induced inflammation in the pleural cavity. Eur Respir J. 12(6):1419–1423.

Vanderhyden BC, Shaw TJ, Ethier JF. 2003. Animal models of ovarian cancer. Reprod Biol Endocrinol. 1:67.

Venter PF, Iturralde M. 1979. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. S Afr Med J. 55(23):917-919.

Wadaan MAM. 2009. Effects of repeated exposure to talcum powder on rabbit skin. Indian J Appl Pure Biol. 24(1):111-115.

Wagner JC, Berry G, Cooke TJ, Hill RJ, Pooley FD, Skidmore JW. 1977. Animal experiments with talc. Inhaled Particles. 4 Pt 2:647-654.

Warheit, DB, Kreiling R, Levy LS. 2016. Relevance of the rat lung tumor response to particle overload for human risk assessment-Update and interpretation of new data since ILSI 2000. Toxicology. 374:42-59.

Webb PM, Jordan SJ. 2017. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 41:3-14.

Weed DL, Gorelic LS. 1996. The practice of causal inference in cancer epidemiology. Cancer Epidemiology, Biomarkers & Prevention. 5:303-311.

Wehner AP, Tanner TM, Buschbom RL. 1977a. Absorption of ingested talc by hamsters. Food Cosmet Toxicol.15(5):453-455.

Wehner AP, Wilkerson CL, Cannon WC, Buschbom RL, Tanner TM. 1977b. Pulmonary deposition, translocation and clearance of inhaled neutron-activated talc in hamsters. Food Cosmet Toxicol.15(5):213-224.

Wehner AP, Hall AS, Weller RE, Lepel EA, Schirmer RE. 1985. Do particles translocate from the vagina to the oviducts and beyond? Food Chem Toxicol. 23(3):367-372.

Wehner AP, Weller RE, Lepel EA. 1986. On talc translocation from the vagina to the oviducts and beyond. Food Chem Toxicol. 24(4):329-338.

Wehner AP. 2002. Cosmetic talc should not be listed as a carcinogen: comments on NTP's deliberations to list talc as a carcinogen. Regul Toxicol Pharmacol. 36:40-50.

[WHI] Women's Health Initiative. 2020. Seattle(WA): The Women's Health Initiative. [accessed 2020 August].

Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles DL, Kampert JB, Grosser S, Jung DL, Ballon S, Hendrickson M. 1988. Personal and environmental characteristics related to epithelial ovarian cancer. I. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol. 128(6):1228-1240.

[WHO, UNFPA, FHI] World Health Organization, United Nations Population Fund, Family Health International. 2013. Male latex condom. Specification, prequalification and guidelines for procurement, 2010, revised April 2013. Geneva (CH): World Health Organization. [accessed 2017 Dec 20].

Wild P, Refregier M, Auburtin G, Carton B, Moulin JJ. 1995. Survey of the respiratory health of the workers of a talc producing factory. Occup Environ Med. 52:470-477.

Wild P, Leodolter K, Refregier M, Schmidt H, and Bourgkard E. 2008. Effect of talc dust on respiratory health: results of a longitudinal survey of 378 French and Austrian talc workers. Occup Environ Med. 65: 261-267.

Williams KA, Labidi-Galy SI, Terry KL, Vitonis AF, Welch WR, Goodman A, Cramer DW. 2014. Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. Gynecologic Oncology. 132:542-550.

Wolf J. 2018. Rule 26 Expert Report of Judith Wolf, MD. United States District Court District of New Jersey. MDL No. 16-2738 (FLW) (LHG). [accessed 2020 July].

Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. 1999. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol. 93(3):372-376.

Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. 2009. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer. 124(6):1409-1415.

Wu AH, Pearce CL, Tseng CC, Pike MC. 2015. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. Cancer Epidemiol Biomarkers Prev. 24(7):1094-1100.

Yan B, Wang H, Rabbani ZN, Zhao Y, Li W, Yuan Y, Li F, Dewhirst MW, Li C-Y. 2006. Tumor necrosis factor-α is a potent endogenous mutagen that promotes cellular transformation. Cancer Res. 66(24):11565–11570.

Zazenski R, Ashton WH, Briggs D, Chudkowski M, Kelse JW, MacEachern L, McCarthy EF, Norhauser MA, Roddy MT, Teetsel NM, Wells AB, Gettings SD. 1995. Talc: Occurrence, Characterization, and Consumer Applications. Regul Toxicol Pharmacol. 21(2):218-229.

Zeng F, Wei H, Yeoh E, Zhang Z, Ren ZF, Colditz GA, Tworoger SS, Su X. 2016. Inflammatory markers of CRP, IL6, TNFα, and soluble TNFR2 and the risk of ovarian cancer: a meta-analysis of prospective studies. Cancer Epidemiol Biomarkers Prev. 25:8:1231-9.

Zervomanolakis I, Ott HW, Hadziomerovic D, Mattle V, Seeber BE, Virgolini I, Heute D, Kissler S, Leyendecker G, Wildt L. 2007. Physiology of upward transport in the human female genital tract. Ann N Y Acad Sci. 1101:1-20.

# Appendix A. Inhalation exposure estimates

**Table A-1. Respirable air concentrations (mg/m$^3$) as measured in Anderson et al. (2017) and Rasmussen et al. (2019)**

| Product | Subject | Average respirable concentration (mg/m$^3$) (% RSD) | Average concentration (mg/m$^3$) by subject ± SD (% RSD) | Study |
|---|---|---|---|---|
| Body powder | 1 | 1.31 | 1.37 ± 0.87 (63.26) | Anderson et al. 2017 |
| Body powder | 1 | 0.69 | - | Anderson et al. 2017 |
| Body powder | 1 | 2.61 | - | Anderson et al. 2017 |
| Body powder | 1 | 0.87 | - | Anderson et al. 2017 |
| Body powder | 2 | 5.03 | 3.28 ± 1.17 (35.77) | Anderson et al. 2017 |
| Body powder | 2 | 2.7 | - | Anderson et al. 2017 |
| Body powder | 2 | 2.76 | - | Anderson et al. 2017 |
| Body powder | 2 | 2.61 | - | Anderson et al. 2017 |
| Body powder | 3 | 0.35 | 0.44 ± 0.18 (39.68) | Anderson et al. 2017 |
| Body powder | 3 | 0.26 | - | Anderson et al. 2017 |
| Body powder | 3 | 0.66 | - | Anderson et al. 2017 |
| Body powder | 3 | 0.5 | - | Anderson et al. 2017 |
| Body powder | 4 | 1.16 | 0.99 ± 0.32 (32.20) | Anderson et al. 2017 |
| Body powder | 4 | 1.18 | - | Anderson et al. 2017 |
| Body powder | 4 | NR | - | Anderson et al. 2017 |
| Body powder | 4 | 0.62 | - | Anderson et al. 2017 |
| Body powder | 5 | 0.75 | 1.15 ± 0.70 (60.62) | Anderson et al. 2017 |
| Body powder | 5 | 0.68 | - | Anderson et al. 2017 |
| Body powder | 5 | 2.18 | - | Anderson et al. 2017 |
| Body powder | 5 | 1.00 | - | Anderson et al. 2017 |
| Body powder | A | 0.48 | 0.48 ± 0.18 | Rasmussen et al. 2019 |
| Face powder | B | 1.80 | 1.80 ± 0.82 | Rasmussen et al. 2019 |
| Overall average | - | 1.44 (81.68) | 1.36 ± 0.97 (71.51) | Combined |
| Range | - | 0.26 – 5.03 | 0.44 – 3.28 | Combined |

Abbreviations: NR = not reported; mass on filter reported as a negative mass

**Table A-2. Estimated inhalation exposure concentrations from self-care products containing loose powder talc available to consumers**

| Scenario | Talc product conc.[a] | Study[b] conc. (mg/m$^3$) | Tier 1 CA[b] (mg/m$^3$) | ET[c] (hr/d) | EF[d] (d/yr) | ED[e] (yr) | Higher tier EC adjusted[f] (mg/m$^3$) |
|---|---|---|---|---|---|---|---|
| Baby powder, infants | 100% | 1.36 | 1.36 | 0.125 | 365 | 4 | 0.0071 |
| Baby powder, adults | 100% | 1.36 | 1.36 | 0.125 | 365 | 8 | 0.0071 |
| Body powder, adults | 100% | 1.36 | 1.36 | 0.083 | 365 | 68 | 0.0047 |
| Face powder, adults | 100% | 1.36 | 1.36 | 0.083 | 365 | 68 | 0.0047 |
| Foot powder, adults | 97 % | 1.36 | 1.32 | 0.083 | 274 | 68 | 0.0034 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dry hair shampoo, adults | 100 % | 1.36 | 1.36 | 0.083 | 84 | 68 | 0.0011 |

Abbreviations: Conc., concentration; CA, concentration in air per event; ET, exposure time; EF, exposure frequency; ED, exposure duration; EC, adjusted exposure concentration.

[a] Highest concentration of talc found per product type from notifications submitted under the *Cosmetic Regulations* to Health Canada for talc, DPD [modified 2018], email from the Therapeutic Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017, unreferenced; LNHPD [modified 2018], email from the Non-prescription and Natural Health Products Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated March 20, 2017, unreferenced; Fiume et al. 2015; Household Product Database 1993-; CPCat 2014; CPID 2017; SDS Search Tool 2016.

[b] Average by subject from Anderson et al. (2017) and Rasmussen et al. (2019). CA = average study concentration × maximum talc concentration in product.

[c] ET is based on the best and most relevant available data. An exposure time of 5 minutes/application is an estimate based on a number of factors including the duration of the particle cloud measured in Rasmussen et al. (2019) (approximately 1 minute), the average sampling duration of 6 minutes from Anderson et al. (2017), the formation of secondary particle clouds as observed in Rasmussen et al. (2019), Pooley (1972), and by NIOSH in an earlier study on talc cosmetic products (Dement et al. 1972). Therefore, there is a need to account for time spent in the vicinity of where the individual is conducting the activity. The median time spent in the bathroom following a shower or bath as reported in U.S. EPA (2011) in Tables 16-29, 16-32, 16-34 and 16-35 ranges from 1 to 10 minutes, with a median time of 5 minutes for the majority of subgroups. The RIVM cosmetic factsheet uses a default of 5 minutes as the typical time spent in a bathroom (U.S. EPA 2011, RIVM 2006). ET = exposure time/application × number of applications/day if there is more than one application per day, whereby baby powder assumes 1.5 applications/day (CTFA 1983, Health Canada 2020); the rest assume 1 application/day or less.

[d] EF is based on the best and most relevant available data reviewed by Health Canada. Frequency values were assumed to occur daily (1.5 applications/day) for baby powder (CTFA 1983, U.S. EPA 2011, Health Canada 2020). Higher values were available in the literature, but were considered too high as this use is no longer recommended by the American Academy of Pediatrics (2015). One application per day was considered for body powder (Zazenski et al. 1995; U.S. EPA 2011 [Table 17-3, baby powder, adult use]; Burns et al. 2019; Health Canada 2020). One application per day was considered for face powder (Ficheux et al. 2015 [Zazenski et al. 1995, median frequency for loose powder foundation], Health Canada 2020 [facial make-up foundation – powder]) as this was the highest central tendency value (median) from the highest quality study (Ficheux et al. 2015). Foot powder was estimated to be used 0.75 times/day or 274 times/year (Ficheux et al. 2015, Health Canada 2020) as this was the highest central tendency value from the highest quality study available. Dry hair shampoo was estimated to be used 0.23 times/day or 84 times/year (Ficheux et al. 2015, Health Canada 2020) as this was the highest central tendency value from the highest quality study available.

[e] Assumed infant wears diapers up to 4 years, adult exposure to baby powder from diapering children, 4 years per child and assume two children per family (Statistics Canada 2016), adult exposure for body powder, and foot powder (80 years lifetime, 12 years child).

[f] Adjusted exposure concentration is calculated in accordance with Equation 8 in the U.S. EPA 2009 guidance document “Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual,” where EC = (CA × ET × EF × ED)/AT, and AT = averaging time, which is on the basis of ED × 365 days/year × 24 hours/day.