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| **Table S.7. Evidence Integration Summary Judgment: Ovarian Cancer** |
| **Summary of Animal, Human, and Mechanistic Evidence** | **Inference across evidence streams** |
| **Evidence from Studies of Exposed Humans** | *Suggestive Evidence of no association** Higher quality cohort studies largely null
* Positive findings limited substantially by recall bias
* No ovarian lesions or tumors in animal models

Other inferences: * Several animal studies show no translocation of talc from perineum
* Talc particle burden in humans not consistently associated with magnitude of talc use
* Talc is not DNA reactive
* Insufficient evidence supporting an MOA for ovarian carcinogenesis
 |
| **Studies, outcome and confidence** | **Key Findings** | **Factors that increase certainty** | **Factors that decrease certainty** |

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| **Summary strength of evidence judgment** |

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| **Ovarian cancer – Cohort Studies**5 *medium* quality studies | * No significant association with epithelial ovarian cancer overall in 4 studies
* Significantly increased risk of serous ovarian cancer (ever talc use) in 1 study
 | * Temporality established in prospective design
* Large, national cohorts
* Consistently null for epithelial ovarian cancer
* Only significant risk estimate for serous was low magnitude, not replicated
 | * Self-reported talc use; limited measures for some analyses (ever v. never use)
 | Indeterminate  |
| **Ovarian cancer – Case-control studies**15 *low* quality studies11 *medium* quality studies | * Significantly increased risk of overall epithelial ovarian cancer and subtypes in about half of the case-control studies
 | * More precise talc exposure measures in some studies (frequency or duration w/≥3 levels)
 | * No temporality
* Increased likelihood of recall/reporting bias (self report after exposure)
* Effect estimates of low magnitude
* Lack of dose-response trends
 | Slight |
| **Evidence from *In Vivo* Animal Studies** |
| **Studies, outcomes, and confidence** | **Key Factors** | **Factors that increase certainty** | **Factors that decrease certainty** | **Summary strength of evidence judgment** |
| 4 *high-quality* studies in rats and mice | * No ovarian or other reproductive tract tumors
* Lung tumors observed in one species in one of four studies
 | * Relatively high quality studies
* Consistently null findings for the target organ of interest
* Tumors found largely at doses exceeding MTD
 | * Carcinogenicity at other sites (lung, other tumors w/high spontaneous rates)
 | Evidence against |
| **Mechanistic Evidence or Supplemental Information** |
| **Biological events or pathways (or other information category)** | **Primary evidence evaluated** | **Key findings, interpretation, and limitations** | **Evidence stream summary** |
| Talc translocation from external application into the reproductive tract | * 4 animal studies of intravaginal or intrauterine administration
* 3 small studies of human talc ovarian burden
 | * Vaginal/perineal application in animals: no translocation to ovaries in monkeys, rats
* Low levels of talc in ovaries of humans but few participants and no relation to duration/magnitude of exposure
 | * Animal studies indicate no substantial amounts of externally applied talc will reach the ovary
* Human evidence of talc burden limited/not associated with usage patterns
* Available mechanistic evidence insufficient to support any mode (or modes) of action for talc and reproductive cancers
 |
| Carcinogenic Mechanisms:Chronic Inflammation and genotoxicity | * 3 GLP/*guideline (K=1)* genotoxicity studies
* 2 medium quality (K=2) *in vitro* mechanistic studies in normal and cancerous ovarian cells
 | * Not genotoxic
* Causes inflammation
* High cellular doses > exposure scenarios in humans
* No *in vivo* studies of inflammation or immune-related mechanisms
 |