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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** | |  | | --- | | **Summary strength of evidence judgment** | |
| **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 studies  11 *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 |