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| **Table S.8. Evidence Integration Summary Judgment: Endometrial and Cervical Cancer** | | | | | |
| **Summary of Animal, Human, and Mechanistic Evidence** | | | | | **Inference across evidence streams** |
| **Evidence from Studies of Exposed Humans** | | | | | *Suggestive Evidence of no association (endometrial)*   * Higher quality cohort studies largely null * Positive findings limited substantially by recall bias * No uterine/cervical lesions or tumors in animal models   Other inferences:     * Several animal studies show little translocation of talc from perineum * Talc is not DNA reactive * Insufficient evidence supporting an MOA for ovarian carcinogenesis   *Insufficient Evidence to determine whether a causal association exists (cervical)*   * Null but very limited body of literature (single epidemiological study) * No uterine/cervical tumors in animals   Other Inferences:   * No evidence of translocation to cervix from perineum |
| **Studies, outcome and confidence** | **Key Findings** | **Factors that increase certainty** | **Factors that decrease certainty** | |  | | --- | | **Summary strength of evidence judgment** | |
| *Four high-quality* cohort studies and one *low-quality* case control study | * No overall associations between talc and uterine or cervical cancer * Subgroup analyses identified at least one statistically significant but weak finding | * Relatively high quality cohort studies * Positive results largely limited to ever v. never talc use | * Recall bias likely in the case control study * Very few studies available; including a single study for cervical cancer | Limited evidence of no association |
| **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 uterine 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 * Other 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 | * Vaginal/perineal application in animals: no translocation to uterus in monkeys, rats; some translocation to cervix in monkeys | * Animal studies indicate no substantial amounts of externally applied talc will reach the uterus; some detection of talc in the cervix * 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 |