|  |
| --- |
| **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
 |