Using study evaluation to inform evidence integration: Application in a systematic review of hexavalent chromium male reproductive outcomes

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Study evaluation is used in systematic reviews to identify the strengths and weaknesses of the evidence base in a consistent and transparent manner. These evaluations can be used to inform evidence integration by identifying factors that may affect the reliability and interpretability of the results. Here, we describe how this principle was applied in a systematic review of the male reproductive effects of hexavalent chromium (Cr(VI)).

Methods

Literature search and screening: This evaluation of male reproductive effects was conducted as part of a systematic review of the health effects of Cr(VI) exposure. Studies were identified by searching three online databases (PubMed, Web of Science, Toxline) through May 2016. Title/abstract screening followed by full-text screening was used to identify animal studies meeting the following PECO (Population, Exposure, Comparators, Outcomes) criteria:

- P: Nonhuman mammal (whole organism) of any life stage
- E: Any exposure to Cr(VI) by oral or inhalation routes
- C: Concurrent vehicle control or unmatched control group
- O: All cancer outcomes; noncancer outcomes in relevant target systems

The literature search identified 23 animal toxicology studies that examined effects on the male reproductive system. Studies included evaluation of:

- Male fertility
- Sperm parameters
- Reproductive hormones
- Sexual behavior

Study evaluation:

- Each of these studies was evaluated by at least two independent reviewers for reporting quality of bias, and sensitivity using the domain-based approach outlined in Figure 1. Based on the results of the evaluation, each study was rated overall as high confidence, medium confidence, low confidence, or uninformative. Evaluations were performed on an outcome-specific basis, as the utility of a study may vary across outcomes.

Results

Table 1. Study evaluation results. These results represent the composite ratings for male reproductive outcomes within each evaluation domain; there were some instances where outcomes within the same study were rated differently due to outcome-specific concerns, in which case an average rating (representative of most outcomes) is shown here. In addition to the 15 studies identified in this analysis, the 8 studies rated uninformative due to serious flaws in the study design (e.g., use of wild-caught animals) or reporting (e.g., data could not be interpreted) and were excluded from consideration.

Summary of effects in high vs. low confidence studies

Figure 3. Incidence of outcomes indicative of male reproductive effects across high and low confidence Cr(VI) animal studies. One high confidence study observed increased testis weight, but otherwise high confidence studies found no evidence of male reproductive effects. Comparative, male reproductive effects were frequently observed in low confidence studies.

Table 2: Evidence profile table for Cr(VI) male reproductive effects

Integration of evidence

Background

It was concluded that animal toxicology studies along with supportive data from mechanistic studies provide strong evidence that Cr(VI) is a male reproductive toxicant. The rationale for this conclusion is summarized in an evidence profile table (Table 2). Relatively severe male reproductive effects were observed across multiple low confidence studies and are supported by mechanistic evidence. However, similar effects were not observed in high confidence studies, and concerns were raised about the potential impact of bias on the interpretation of the results in low confidence studies. Fertility ability to produce offspring was not affected in any studies but this did not affect overall conclusions, since rodents can remain fertile after large reductions in sperm count.

Figure 2. Summary of effects on sperm. Data is shown for all studies for which the ingested dose of Cr(VI) could be calculated. Decreased sperm count, motility, and viability were also observed in the low confidence study by Kumar et al. 2017, but the ingested dose of Cr(VI) could not be calculated based on the reported information.

Summary of Effects:

- High confidence subchronic oral exposure studies in rats and mice (NTP 1996a, 1996b, 2007) and continuous breeding study in mice (NTP 1997) generally indicated that the male reproductive system is not affected by Cr(VI) exposure.
- Low confidence oral exposure studies consistently observed effects on sperm quality and quantity, testicular histopathology, male reproductive organ weights, hormone levels, sexual behavior, and AGD.
- As an example, Figure 2 summarizes effects on sperm parameters across studies.
- Biological plausibility for male reproductive effects of Cr(VI) exposure was supported by mechanistic studies (in vivo and in vitro) demonstrating oxidative stress and apoptosis in male reproductive tissues, altered steroidogenic signaling, disruption of the blood-testis barrier, and alterations in melatonin.
- No effects were observed in three low confidence inhalation studies.

Evidence synthesis: Evidence was synthesized across studies, using the following considerations to articulate the strengths and weaknesses of the database: consistency, biological gradient (dose response), strength (effect magnitude) and precision, biological plausibility, and coherence. Careful examination was given to the potential impacts of risk of bias and sensitivity on the conclusions. Relevant mechanistic data identified in the literature search was considered as part of the weight of evidence for biological plausibility.

Figure 1. Study evaluation process

Evidence for evidence synthesis included all studies with data available.

Summary of study outcomes:

- Incidence of outcomes in high and low confidence studies
- Biological endpoints
- Mechanistic endpoints
- Other endpoints

Bibliography

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