

### **Instructions for answering study evaluation domains**

Study evaluations are performed on an endpoint/outcome-specific basis. For each evaluation domain, core and prompting questions are provided to guide the reviewer in assessing different aspects of study design and conduct related to reporting, risk of bias and study sensitivity. For some domains (see below), additional outcome- or chemical-specific refinements to the criteria used to answer the questions should be developed *a priori* by reviewers. Each domain receives a judgment of *Good*, *Adequate*, *Deficient*, *Not Reported* or *Critically Deficient* accompanied by the rationale and primary study-specific information supporting the judgment. Once all domains are evaluated, a confidence rating of *High*, *Medium*, or *Low* confidence or *Uninformative* is assigned for each endpoint/outcome from the study. The overall confidence rating should, to the extent possible, reflect interpretations of the potential influence on the results (including the direction and/or magnitude of influence) across all domains. The rationale supporting the overall confidence rating should be documented clearly and consistently, including a brief description of any important strengths and/or limitations that were identified and their potential impact on the overall confidence.

Note that due to current limitations in HAWC, domain judgments and overall ratings for all individual endpoints/outcomes assessed in a study will need to be entered using a single drop-down selection and free-text box for each study. Thus, all the reviewer decisions (and the supporting rationale) drawn at the level of a specific cohort or individual endpoint within a study must be described within a single free-text box. Within the text boxes, please remember to call out each of the specific judgments and rationales. A good form to follow for the text boxes is '**Endpoint/Outcome – Judgment – Rationale**'. When selecting the representative rating for the domains and overall rating (i.e., the drop-down selection with the associated color code), it is typically most appropriate to select the judgment that best represents an average of the responses for the endpoint/outcome evaluated in that study, considering the pre-defined importance of individual outcomes/health effects to the assessment (see Overall Confidence examples).

### **Example answers for evaluating the domains related to experimental animal toxicology studies**

#### **Reporting [provide judgement and rationale for the study]**

<b>Good</b>	<b>Good.</b> Important information is provided for test species, strain, sex, age, exposure methods, experimental design, endpoint evaluations and the presentation of results. The authors report that “the study was conducted in compliance with the OECD guidelines for Good Laboratory Practice [c(81) 30 (Final)]”.
<b>Adequate</b>	<b>Adequate.</b> All critical information is reported but some important information is missing. Specifically, it is unclear what strain of rats was used.

<b>Deficient</b>	<b>Deficient.</b> All critical information is reported, but some important information is missing that makes additional study evaluation and interpretation of the results difficult. Specifically, it is not reported (and cannot be inferred) what age/lifestage the animals were at outcome evaluation.
<b>Critically Deficient</b>	<b>Example 1: Critically Deficient.</b> Critical information is missing. Authors did not report the duration of the exposure or the results (qualitative or quantitative). <b>Example 2: Critically Deficient.</b> Critical information is missing. The study reports animals were exposed to per-and polyfluoroalkyl substances (PFAS), but the specific chemicals tested were not provided.

**Selection and performance – Allocation [provide judgement and rationale for each cohort/experiment in the study]**

<b>Good</b>	<b>Example 1: Good.</b> The study authors report that "Fifty males and fifty females were randomly assigned to groups by a computer-generated weight-ordered distribution such that individual body weights did not exceed + 20% of the mean weight for each sex."
<b>Adequate</b>	<b>Example 1: Adequate.</b> Randomization was not performed. However, normalization procedures that balance important variables across groups were performed. Specifically, the authors state that animals were "allocated into groups with similar distributions in body weight." <b>Example 2: Adequate.</b> The study authors state that "animals were randomly distributed to exposure groups". However, the specific randomization method used was not described. <b>Example 3: Adequate.</b> Randomization was not explicitly reported. However, the study was performed according to OECD 416 and EPA OPPT 870.3800 guidelines which both specify randomization, although the specific methods of randomization used in the current study could not be inferred. OECD 416 guidelines state "animals should be randomly assigned to the control and treated groups (stratification by body weight is recommended)." The EPA OPPT 870.3800 guidelines state "animals should be randomly assigned to the control and treatment groups, in a manner which results in comparable mean body weight values among all groups."

	<b>Example 4: Adequate.</b> The study authors state that "Animals were randomized by weight into treatment groups," and do not present the specific randomization procedural details.
<b>Not reported (interpreted as deficient)</b>	<b>Not reported (interpreted as deficient).</b> The authors did not indicate randomization or other normalization procedures for balancing important variables across groups.
<b>Critically deficient (rare)</b>	<b>Critically deficient.</b> There is direct evidence that animals were allocated to treatment groups in a subjective way, involving the judgment of the investigator. Specifically, the study authors report "the heavier dams were assigned to the higher dose groups to reduce toxicity from [chemical]"; dam weight is an important variable for these developmental outcomes.

**Selection and performance – Observational bias/Blinding [provide judgement and rationale for each endpoint or groups of endpoints]**

<b>Good</b>	<p><b>Example 1: Good. <u>Histopathology</u>:</b> Although the study did not indicate blinding, blinding during the initial evaluation of tissues for initial or non-targeted evaluations is generally not recommended as masked evaluation can make the task of separating treatment-related changes from normal variation more difficult and may result in subtle lesions being overlooked (Crissman, 2004). The study did include a secondary evaluation by a pathology working group (PWG) review on coded pathology slides which minimized the potential for observational bias.</p> <p><b>Example 2: Good. <u>Organ weights, FOB, motor activity, swim maze and histopathology</u>:</b> Authors reported that the investigators were blinded to the animal treatment group during evaluation for all outcome measures (i.e.). Although blinding is not recommended for initial or non-targeted evaluations (Crissman, 2004), this study evaluated prespecified outcomes in targeted evaluations for which blinding is appropriate (cell counts in the CA3 region of the hippocampus).</p>
<b>Adequate</b>	<b>Adequate. <u>Histopathology measures</u>:</b> Authors report "lesions were counted by 2 observers in a blinded fashion" although it should be noted that blinding during the initial evaluation of tissues is generally not recommended for initial or non-targeted evaluations as masked evaluation can make the task of separating treatment-related changes from normal variation more difficult and may result in subtle lesions being overlooked (Crissman, 2004).

<p><b>Not reported (interpreted as adequate)</b></p>	<p><b>Example 1: Not reported (interpreted as adequate).</b> <u>Body and organ weights, developmental landmarks, and hormone measures:</u> Authors did not indicate whether investigators were blinded during outcome assessment. Potential concern for bias was mitigated for these endpoints which were measured using automated/computer driven systems, standard laboratory kits, relatively simple, objective measures (e.g., body or tissue weight)</p> <p><b>Example 2: Not reported (interpreted as adequate).</b> <u>Histopathology:</u> Blinding during the initial evaluation of tissues is generally not recommended as masked evaluation can make the task of separating treatment-related changes from normal variation more difficult and may result in subtle lesions being overlooked (Crissman, 2004). Histopathology was evaluated by an independent laboratory (Toxicology Pathology Associates Little Rock, Arkansas, John Pletcher, D.V.M., DACPV). No subsequent steps to minimize the potential for observational bias were reported (i.e., conducting a secondary targeted blinded review, independent prospective or retrospective peer-review, formation of a pathology working group).</p> <p><b>Example 3: Not reported (interpreted as adequate).</b> <u>Fetal evaluation for malformations:</u> Blinding during initial evaluation of fetuses is typically not conducted as masked evaluation can make the task of separating treatment-related changes from normal developmental variation more difficult and may result in subtle developmental anomalies being overlooked. Fetal evaluations were conducted in accordance with regulatory test guideline recommendations, using standardized nomenclature. No subsequent steps to minimize the potential for observational bias were reported (e.g., conducting a secondary targeted blinded review, or an independent prospective or retrospective peer-review).</p>
<p><b>Not reported (interpreted as deficient)</b></p>	<p><b>Not reported (interpreted as adequate).</b> <u>Neurobehavior (auditory and visual sensory reactivity):</u> Procedural methods addressing observational bias were not described for these endpoints, which were measured using highly subjective methods (i.e., it appears that investigators measured reactivity using manually operated timers).</p>
<p><b>Critically deficient (exceedingly rare)</b></p>	<p><b>Critically deficient.</b> <u>Neurobehavior after restraint stress:</u> There is direct evidence of observational bias in testing methods. Specifically, the study reported that, to minimize stress from changing investigators across trials,</p>

	one investigator consistently stressed control mice each day for 30 minutes and subsequently tested behaviors, while a separate investigator conducted stress and behavioral testing in treated mice. There was no mention of blinding of investigators.
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***Confounding/variable control [provide judgement and rationale for each cohort/experiment in the study, specifying when the potential for confounding is restricted to, or of greater concern for, particular endpoints]***

<b><i>Good</i></b>	<b>Good.</b> Based on the study report, vehicle (deionized water with 2% tween 80) and husbandry practices were inferred to be the same in controls and treatment groups. The experimental conditions described provided no indication of concern for uncontrolled variables or different practices across groups.
<b><i>Adequate</i></b>	<b>Example 1 (oral): Adequate.</b> <u>Hormone measurements</u> : Authors did not use a soy-free diet. Soy-based rodent feeds contain phytoestrogens that may act as a confounder for endocrine-related measures. Since this study includes relatively high doses (100 and 1500 mg/kg-d) the concern is minimal. <b>Example 2 (inhalation): Adequate.</b> <u>Behavior, immunological responses, and hormonal changes</u> : control rats did not appear to receive chamber air exposures (they were left in their home cages). As this might introduce a difference in stressors across groups, this difference is interpreted as a possible confounder for measures shown to be sensitive to stress, although the impact of this limitation on the results is expected to be minimal.
<b><i>Deficient</i></b>	<b>Deficient.</b> Dams in the medium and high exposure groups (1500 and 15,000 ppm, respectively) showed significantly lower consumption of the treated food throughout the exposure period (gestation) that increased to control levels after the exposure ended. Addition of the test chemical may have affected the palatability of the food and reduced food intake during gestation may have significantly impacted the developmental outcomes in the pups.
<b><i>Critically deficient</i></b>	<b>Critically deficient.</b> The study did not include a vehicle-only control group, and, given the high concentration of DMSO required to solubilize the test article in other experiments using a similar exposure design, this is interpreted as likely to be a significant driver of any observed effects.

**Reporting and attrition bias [provide judgement and rationale for each cohort/experiment in the study]**

<b>Good</b>	<b>Good.</b> Animal loss was reported (the authors treated 10 rats/sex/dose group and noted one death in a high-dose male rat at day 85 of study). All endpoints described in methods were reported qualitatively or quantitatively.
<b>Adequate</b>	<b>Adequate.</b> Animal loss occurred and was reported (see below), but these are not expected to significantly impact the interpretation of the results.* All endpoints described in methods were reported qualitatively or quantitatively. “In the high dose (1000 mg/kg-day) group no male animals were able to complete the entire study; whereas all male rats exposed at other doses completed the 4-week experiment. In the female group, 1 rat was removed in the 250 mg/kg-day group at day 25, 1 rat in the 500 mg/kg-day was removed at day 21 and 8 rats in the 1000 mg/kg/day group were removed between days 16 and 27 of the experiment.” Justification for removals was provided by the study authors.
<b>Deficient</b>	<b>Example 1: Deficient.</b> Unaccounted for loss of animals was difficult to assess because the study authors do not provide a clear description of the number of animals per exposure group or the selection of animals for outcome analysis. Table 1 states there were 8 animals used in experiment 1 and 6 animals used in experiments 2 and 3. The figures and tables report data for varying numbers of animals (from 4 to 8), but the authors do not provide a description of the approach used to sample animals for each outcome. <sup>1</sup> <b>Example 2: Deficient.</b> Although the authors indicated that “the liver, kidneys, and spleen were weighed and processed for routine histopathology at study termination”, qualitative or quantitative findings were not reported for liver or kidney weights, nor for liver, kidney, or spleen histopathology (“spleen weights” were described as unchanged during the description of changes in cultured splenic immune cells).
<b>Critically Deficient</b>	<b>Critically deficient.</b> None of the animals in the high and medium dose groups survived and there was high mortality (>75%) in the low dose group.

**Exposure methods sensitivity - Chemical administration and characterization [provide judgement and rationale for each cohort/experiment in the study]**

<p><b>Good</b></p>	<p><b>Example 1 (oral): Good.</b> Source (3M) and purity (98%) are described, and the authors provided verification using analytical methods (GC/MS). Addressing concerns about known instability in solution for this chemical, the authors verified the dosing solutions twice weekly over the course of the experiment. Animals were exposed via gavage with all dose groups receiving the same volume.</p> <p><b>Example 2 (inhalation): Good.</b> Source (3M) and purity (98%) of the test article are described. All animals were transferred to dynamic inhalation exposure chambers for the exposures. The concentration of the test chemical in the air was continuously monitored from the animals' breathing zone throughout the 6-hour exposure periods and mean daily average concentrations and variability were reported.</p>
<p><b>Adequate</b></p>	<p><b>Example 1 (oral): Adequate.</b> Purity (98%) is described, but source is missing. Purity is assumed to be vendor reported because independent analytical verification of the purity is not described. Authors were contacted to try to obtain the vendor information however they did not respond. Stability assessments were not necessary because fresh dosing solutions were prepared daily.</p> <p><b>Example 2 (inhalation): Adequate.</b> Source (3M) and purity (98%) of the test article are described. All animals were transferred to dynamic inhalation exposure chambers for the exposures. The nominal/target concentrations of the test chemical were not verified by analytical measurements of the chamber air.*</p>
<p><b>Deficient</b></p>	<p><b>Example 1 (oral): Deficient.</b> Test chemical supplied by the chemical manufacturer. Purity and isomeric composition is not described and could not be obtained from manufacturer's website. Analytical verification of the test article's purity and composition was not provided, and the stability of chemical in the diet across the 1-year exposure period does not appear to have been assessed.</p> <p><b>Example 2 (inhalation): Deficient.</b> Source (3M) and vendor-reported purity are described, although these were not independently verified. The animals appear to have been exposed in static (i.e., without dynamic</p>

	airflow) chambers; this is not interpreted as a critical deficiency due to the relatively short (2-hour) durations of daily exposure.
<b>Critically Deficient</b>	<p><b>Example 1 (oral): Critically deficient.</b> The test article contains large amounts of a known impurity [specify] that has previously been shown to cause the outcome(s) of interest. Based on the doses tested (and inferences regarding the administered doses of the impurity), this is likely to be a significant driver of any observed effects.</p> <p><b>Example 2 (inhalation): Critically deficient.</b> Dams were exposed in static chambers during gestation, and there was evidence of overt toxicity (i.e., gasping) throughout the 12-hr daily exposures at all tested concentrations. This is likely to be a substantial driver of any observed developmental effects.</p>

**Exposure methods sensitivity – Exposure timing, frequency, and duration [provide judgement and rationale for each endpoint or groups of endpoints]**

<b>Good</b>	<p><b>Example 1: Good.</b> Study uses a standard OECD short-term (28-day) study design to examine toxicological effects that are routinely evaluated in this testing guideline.</p> <p><b>Example 2: Good.</b> The experimental design and exposure period were appropriate for evaluation of potential male reproductive and developmental effects. The experiment was designed to evaluate reproductive and developmental outcomes and followed recommendations in <a href="#">OECD 416</a> and <a href="#">EPA OPPT 870.3800</a> guidelines.</p>
<b>Adequate</b>	<p><b>Adequate.</b> The study does not include the full developmental window of exposure most informative to evaluating potential effects on androgen-dependent development of male reproductive organs. Specifically, the study exposed rats from GD18-GD21, whereas the critical window for the development of these endpoints (i.e., cryptorchidism; testes and seminal vesicle weights; and male reproductive organ histopathology) begins on GD15, and peaks around GD17 (NRC 2008 [635834]; Scott et al 2009 [673313]) in rats. The incomplete coverage of this critical window in this study is expected to result in a minor bias towards the null.</p>
<b>Deficient</b>	<p><b>Deficient.</b> The experimental design is not considered appropriate for evaluation of male fertility. Male rats were exposed for <i>chemical X</i> for 1 week and fertility was assessed on week 2 of the study. This design is considered deficient because in most rodent species “damage to</p>

	spermatogonial stem cells will not appear in samples from the cauda epididymis or in ejaculates for 8 to 14 weeks” ( <a href="#">US EPA 1996</a> ).
<b>Critically Deficient</b>	<b>Critically deficient.</b> The experimental design is not appropriate for evaluation of cancer endpoints. Animals were necropsied and tissues evaluated for the presence of tumors and/or neoplasms 4 weeks after only a 28-day exposure period. Notably, because this critical deficiency is due to insensitivity, depending on other identified limitations, the utility of this study will depend on whether effects were observed in the study (i.e., if tumors were observed, this study could be adjusted to a higher rating)

**Outcome measures and results display - Endpoint sensitivity and specificity [provide judgement and rationale for each endpoint or groups of endpoints]**

<b>Good</b>	<p><b>Example 1: Good.</b> <u>Lipid/Lipoproteins</u>: There are no notable concerns about aspects of the procedures, or for the timing of these evaluations. Study authors used standard methodology (i.e., commercial kits) appropriate for use in adult liver tissue samples.</p> <p><b>Example 2: Good.</b> <u>Organ weight, body weights, and hormone measures</u>: no concerns regarding the specificity and validity of the protocols and measures were identified. Study authors used standard methodology for evaluating organ and body weights. Thyroid hormones were measured using commercial electrochemiluminescence-immunoassay methods, and the known diurnal variation in these measures was accounted for during blood collection.</p>
<b>Adequate</b>	<p><b>Example 1: Adequate.</b> <u>Histopathology</u>: Tissues were fixed in 10% neutral buffered formalin, trimmed, sectioned (5 microns) and embedded and stained with H&amp;E. Evaluations included 12 tissues from all animals in the control and highest dose groups. Although not explicitly stated, it is inferred that tissues from animals in the low- and mid-dose groups would have been evaluated if significant increases in lesion incidence were observed at the highest dose. This practice is consistent with NTP pathology guidelines (ref) and is expected to be of minimal concern unless effects are observed at the high dose. Additionally, the report did not provide information on sampling (e.g., # sections evaluated/tissue, sections evaluated at x micron or section intervals). Together, the missing study details introduce some concern for potential insensitivity.</p>

	<p><b>Example 2: Adequate.</b> <u>Clinical chemistry</u>: Some concern was raised regarding the procedural methods, as no information was provided on the diagnostic kits and, for some of the specific measures (i.e., those without specific data reported), it is unclear whether serum or plasma was analyzed.</p>
<b>Deficient</b>	<p><b>Example 1: Deficient.</b> <u>Histopathology (testis)</u>: Concerns regarding the method used to preserve testis for histological analysis: 10% formalin. For evaluation of histopathological effects in the testis, conventional immersion fixation in buffered formalin is not recommended as it gives very poor penetration of fixative, and may result in artifacts (Haschek (ed) et al 2009 [3987435]; Foley et al 2001 [PMID: 11215684]).</p> <p><b>Example 2: Deficient.</b> <u>Nipple retention</u>: Concerns for insensitivity were raised due to the timing of endpoint evaluation. Specifically, the authors examined nipple retention in rats at PND 9, whereas this endpoint is more appropriately evaluated around PNDs 12-14.</p> <p><b>Example 3: Deficient.</b> <u>Motor activity</u>: Concerns were raised regarding the small sample sizes used to evaluate these outcomes. Specifically, the authors tested 4 animals (sex not specified, but assumed males) per group. Ideally, it is preferable to have more than 10 animals/sex/ group for this type of evaluation, according to OECD guidelines.</p>
<b>Critically Deficient</b>	<p><b>Critically deficient.</b> [<u>Endpoint name</u>]: [Assay X] has been shown to be unreliable for evaluating [endpoint of interest]. Currently best practice is to use [Assay Y] for this endpoint.</p>

**Outcome measures and results display - Results presentation [provide judgement and rationale for each endpoint or groups of endpoints]**

<b>Good</b>	<p><b>Good.</b> There are no notable concerns about the way the results are analyzed or presented.</p>
<b>Adequate</b>	<p><b>Example 1: Adequate.</b> <u>Reproductive organ weights, hormone measures</u>: results are presented graphically; however, the authors do not clarify whether error bars correspond to SD or SE.</p> <p><b>Example 2: Adequate.</b> <u>Developmental effects</u>: the study failed to report information on potential maternal toxicity; however, all tested doses other than the highest dose are not expected to cause overt toxicity in adults, reducing the level of concern.</p>

	<p><b>Example 3: Adequate.</b> <u>Anogenital distance (AGD)</u>: The authors reported AGD without adjusting for body weight, which is preferred (Daston 1998 [3393032]). However, because the study also provided body weight data, approximation was possible, limiting concern.</p>
<b>Deficient</b>	<p><b>Example 1: Deficient.</b> <u>Histopathology</u>: Incidence and severity of individual effects was unclear, as only scores across multiple, disparate pathological endpoints were reported.</p> <p><b>Example 2: Deficient.</b> <u>Behavior (neuromuscular function and dexterity)</u>: Performance on the rotarod was presented as incidence of falling off the rod within an arbitrary time, rather than as time spent on the rod (the preferred metric). This dichotomization of continuous data without sound justification is expected to strongly bias the results towards observing an effect.</p> <p><b>Example 3: Deficient.</b> <u>Brain weight</u>: Authors presented only relative brain weights, and absolute weights could not be calculated. The adult CNS is highly protected, and absolute brain weight data are preferred [include reference].</p> <p><b>Example 4: Deficient.</b> <u>Birth outcomes</u>: Data on pup viability, weights, and malformations were reported as pup averages, without addressing potential litter effects.</p>
<b>Critically Deficient</b>	<p><b>Critically deficient.</b> <u>Endpoint name</u>: The study presents the results for this endpoint in both a table and figure; however, the data do not match (e.g., mean <math>\pm</math> SE reported for the control group is <math>2.3 \pm 0.5</math> in the table and <math>1.9 \pm 0.2</math> in the figure). This reporting discrepancy could not be resolved from the information provided in the study and study authors did not respond to queries for clarification.</p>

**Overall confidence [provide judgement and rationale for each endpoint or groups of endpoints]**

<b>High confidence</b>	<p><b>High confidence.</b> <u>Reproductive and developmental effects other than behavior</u>: The study was well-designed for the evaluation reproductive and developmental toxicity induced by chemical exposure. The study applied established approaches, recommendations, and best practices, and employed an appropriate exposure design for these endpoints. Evidence was presented clearly and transparently.</p>
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	<p><b>Low confidence.</b> <u>Behavioral measures</u>: The cursory cage-side observations of activity are considered insensitive and non-specific methods for detecting motor effects, with a strong bias towards the null.</p>
<b>Medium confidence</b>	<p><b>Medium Confidence.</b> <u>Developmental effects</u>: The study was adequately designed for the evaluation of developmental toxicity. Although the authors failed to describe randomized allocation of animals to exposure groups and some concerns were raised regarding the sensitivity (i.e., timing) and sample sizes (i.e., n=6 litters/group) used for the evaluation of potential effects on male reproductive system development with gestational exposure, these limitations are expected to have a minimal impact on the results.</p>
<b>Low confidence)</b>	<p><b>Low confidence.</b> <u>Developmental effects</u>: Substantial concerns were raised regarding quantitative analyses without addressing potential litter effects. Other significant limitations included incomplete data presentation (sample sizes for outcome assessment were unclear; no information on maternal toxicity was provided), and methods for selection of animals for outcome assessment.</p> <p><b>Medium Confidence.</b> <u>Histopathology</u>: The study authors did not report information on the severity of histological effects for which this is routinely provided. The authors also failed to describe use of methods to reduce potential observational bias.</p> <p><b>Uninformative.</b> <u>Sperm Measures</u>: Issues were identified with the methods used to prepare samples for analysis, which are likely to introduce artifacts. Concerns were also raised regarding results presentation (i.e., lack of group variability), missing information on sample sizes and loss of animals, and a lack of information on the timing of these evaluations. Taken together, the evaluation of this endpoint was considered uninformative.</p>
<b>Uninformative</b>	<p><b>Example 1: Uninformative.</b> Critical information was not reported. Specifically, the study authors did not report the duration of the exposure or the results (qualitative or quantitative). Given this critical deficiency, the other domains were not evaluated.</p> <p><b>Example 2: Uninformative.</b> Concerns were raised over the lack of information on test animal strain and allocation, and chemical source/purity. The lack of information on blinding or other methods to reduce observational blinding is also of significant concern for the</p>

	endpoints of interest (i.e., follicle counts, ova counts, and evaluation of estrous cyclicity). Finally, concerns were also raised over the apparent self-plagiarism in similar chromium studies published in 1996 by this group of authors. Taken together, this combination of limitations resulted in an interpretation that the results were unreliable.
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\*Note to assessment teams: This information should be carried forward to evidence synthesis, as this represents an important consideration for decisions to advance studies for dose-response analysis.