The evidence profile table is a tool that complements the evidence integration narrative for human and animal data. Explanations for factors that increase or decrease confidence are provided in summaries.

### HUMAN STUDIES

**Testosterone (adult)**

- **Quality of evidence:**
  - All cross-sectional studies: High
  - Small cross-sectional studies: Robust
  - Longitudinal studies: Robust
  - Animal studies: Robust

- **Factors that increase confidence:**
  - Consistency
  - Exposure-response gradient
  - Effect size
  - Biological plausibility
  - Minimal risk of bias

- **Factors that decrease confidence:**
  - Few studies available

- **Summary of findings:**
  - Based on data for testosterone in adults, supported by slight evidence in other outcomes with low sensitivity and few available studies explaining lack of clear associations.

- **Within-stream evidence judgment:**
  - Robust

### ANIMAL STUDIES

**Gestational exposure**

- **Testosterone**

- **Quality of evidence:**
  - High confidence
  - Medium confidence
  - Low confidence

- **Factors that increase confidence:**
  - Consistency
  - Exposure-response gradient
  - Effect size
  - Biological plausibility
  - Minimal risk of bias

- **Factors that decrease confidence:**
  - Few studies available

- **Summary of findings:**
  - A dose-related decrease in testicular androgen levels or production (up to 46% compared to control) was observed in all studies in rats and mice that evaluated this endpoint. Several of these studies also demonstrated decreased testicular expression of genes and proteins in the androgen receptor pathway, which provides support for biological plausibility.

- **Within-stream evidence judgment:**
  - Robust

**Male morphological development**

- **Testosterone**

- **Quality of evidence:**
  - High confidence
  - Medium confidence
  - Low confidence

- **Factors that increase confidence:**
  - Consistency within rat studies
  - Exposure-response gradient
  - Effect size
  - Biological plausibility
  - Minimal risk of bias

- **Factors that decrease confidence:**
  - Few studies available

- **Summary of findings:**
  - All rat studies observed a dose-related increase in effects consistent with decreased testosterone and INSL-3, including increased time to puberty, decreased AGD, nipple retention, cryptorchidism, hypospadias, expressed as penis, and clitoral prepuce. No effects on AGD were observed in mice (Wang et al. 2017).

- **Within-stream evidence judgment:**
  - Robust

**Sperm evaluation and histopathological effects in testis or epididymis**

- **Testosterone**

- **Quality of evidence:**
  - High confidence
  - Medium confidence
  - Low confidence

- **Factors that increase confidence:**
  - Consistency
  - Exposure-response gradient
  - Effect size
  - Biological plausibility
  - Minimal risk of bias

- **Factors that decrease confidence:**
  - Few studies available

- **Summary of findings:**
  - Adverse effects on the testis and/or sperm were observed in rats and mice, including a dose-related increased incidence of pathological lesions of the testis (Borch et al. 2006, Saillenfait et al. 2008), epididymal steatosis, and azoospermia (Saillenfait et al. 2008), and decreased sperm concentration and motility (Wang et al. 2017).

- **Within-stream evidence judgment:**
  - Robust

**Reproductive organ weight**

- **Testosterone**

- **Quality of evidence:**
  - High confidence
  - Medium confidence
  - Low confidence

- **Factors that increase confidence:**
  - Exposure-response gradient
  - Biological plausibility
  - Minimal risk of bias

- **Factors that decrease confidence:**
  - Few studies available

- **Summary of findings:**
  - Decreased reproductive organ weights were observed in rats (Saillenfait et al. 2008), whereas a consistent trend in testis weight was not observed in mice (Wang et al. 2017).

- **Within-stream evidence judgment:**
  - Moderate

**Postnatal exposure**

- **Testosterone**

- **Quality of evidence:**
  - Low confidence
  - Medium confidence
  - High confidence

- **Factors that increase confidence:**
  - Consistency
  - Biological plausibility
  - Coherence with gestational exposure studies
  - High risk of bias
  - Few studies available

- **Factors that decrease confidence:**
  - Few studies available

- **Summary of findings:**
  - Rats were found to have increased testicular atrophy (Foster et al. 1981) and decreased spermatozoa and spermatogenesis (Oishi and Hiraga 1980b). Dehydrotestosterone (DHT) and estradiol (E2) from the perinatal environment were also associated with reduced testicular weights (Foster et al. 1981).

- **Within-stream evidence judgment:**
  - Indeterminate

**Comparison with findings from the National Academy of Sciences (NAS) systematic review of the low-dose toxicity of phthalates (2017)**

Table 1: Summary of conclusions for DIBP from NAS 2017.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Initial hazard evaluation</th>
<th>Testosterone</th>
<th>Hypogonadism</th>
<th>AGD</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>Presumed human hazard</td>
<td>Based on high level of evidence from animal studies and inadequate evidence from human studies</td>
<td>Not classifiable</td>
<td>Not classifiable</td>
<td>Based on inadequate evidence from human and animal studies</td>
</tr>
<tr>
<td>AGD</td>
<td>Not classifiable</td>
<td>Based on inadequate evidence from human and animal studies</td>
<td>Not classifiable</td>
<td>Based on inadequate evidence from human and animal studies</td>
<td></td>
</tr>
</tbody>
</table>

Both IRIS and NAS (2017) concluded that DIBP is likely to cause male reproductive toxicity in humans. However:

- NAS was only able to draw this conclusion for testosterone, based on the high level of evidence from rodent studies. Other endpoints (AGD and hypogonadism) were determined to have inadequate evidence available.
- The IRIS systematic review was broader in scope (see Table 2) and was able to draw conclusions for a range of androgen-dependent and -independent male reproductive outcomes.

Table 2: Summary of major scoping differences between the IRIS and NAS systematic reviews of DIBP

<table>
<thead>
<tr>
<th>IRIS</th>
<th>NAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>All life stages and dose levels</td>
</tr>
<tr>
<td>In utero exposure</td>
<td>Animals using a single dose ≤500 μg/kg-day are excluded.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Male reproductive outcome</td>
</tr>
</tbody>
</table>