GreenScreen® Framework and Endocrine Activity: An Analysis of 1,000 GreenScreen® Assessments

mwhittaker@toxservices.com
GreenScreen® classifies chemicals against 18 hazard endpoints to derive a Benchmark score, with BM-1 being worst and BM-4 being best. BM-U is possible, too, if there are numerous data gaps.

**GreenScreen® Benchmark Scoring**

- **Benchmark 4**: Prefer – Safer Chemical
- **Benchmark 3**: Use but Still Opportunity for Improvement
- **Benchmark 2**: Use but Search for Safer Substitutes
- **Benchmark 1**: Avoid – Chemical of High Concern

**GreenScreen® Benchmark Distribution To Date**

- BM-1: 18.37%
- BM-2: 52.11%
- BM-3: 8.61%
- BM-3DG: 4.13%
- BM-4: 0.00%
- BM-U: 10.54%
- Stratified: 1.93%
- LT-1: 0.79%
- BM-1TP: 2.37%
- BM-2TP: 0.79%
- BM-2DG: 1.14%

Legend:
- BM-1
- LT-1
- BM-1TP
- BM-2TP
- BM-2
- BM-3
- BM-3DG
- BM-4
- BM-U
- Stratified
Endocrine Activity: Relation to GreenScreen® Benchmark Scores

Endocrine Activity hazard classification:

- **Low**
  - Benchmark 4: Prefer – Safer Chemical
  - Benchmark 3: Use but Still Opportunity for Improvement
  - Benchmark 2: Use but Search for Safer Substitutes
  - Benchmark 1: Avoid – Chemical of High Concern

- **Moderate** OR **Data Gap**

- **High** OR **Data Gap**

Low OR Data Gap

Moderate OR Data Gap

High OR Data Gap
What Triggers Hazard Scores for Endocrine Activity in a GreenScreen® Assessment?

- GreenScreen® implements a two-step hazard classification process for endocrine activity.

- What is usually scored:
  - **Moderate** hazard score for endocrine activity is triggered by any evidence of endocrine activity: often changes in hormone levels, histopathological changes in endocrine organs, and/or in vitro data.
  - **High** endocrine activity hazard scores are only assigned when endocrine activity is associated with plausibly related High hazard scores for other human health endpoints.
    - Most often reproductive or developmental, less often carcinogenicity or systemic toxicity.

| Evidence of endocrine activity + no plausibly related hazard classification | Final Score | Moderate |
| Evidence of endocrine activity + **Moderate** plausibly related hazard endpoint classification | Final Score | Moderate |
| Evidence of endocrine activity + **High** plausibly related hazard endpoint classification | Final Score | High |
• GreenScreen®’s birthday is March 20, 2007
• GreenScreen® has undergone four major revisions (v. 1.0 – 1.4)
**GreenScreen®: Version 1.0**

- **Version 1.0 GreenScreen®**
  - Endocrine disruption was one of the assessed hazard endpoints
  - >90% of v. 1.0 GreenScreens® had a data gap endocrine disruption

### Endocrine Disruption Score (V. 1.0)

<table>
<thead>
<tr>
<th>Hazard</th>
<th>Very High (v)</th>
<th>High (H)</th>
<th>Moderate (M)</th>
<th>Low (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Disruption*</td>
<td>- Evidence of adverse effects in humans; or</td>
<td>- Evidence of adverse effects in humans; or</td>
<td>- Suggestive animal studies;</td>
<td>No basis for concern identified</td>
</tr>
<tr>
<td></td>
<td>- Weight of evidence demonstrates that mechanisms of action lead to adverse effects</td>
<td>- Weight of evidence demonstrates that mechanisms of action lead to adverse effects</td>
<td>- Analog data;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Chemical class known to produce toxicity;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- EU Draft List - Category 1 or 2; or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Japanese list</td>
<td></td>
</tr>
</tbody>
</table>

**Human Health Effects**

<table>
<thead>
<tr>
<th>Priority Effects</th>
<th>Carcinogenic</th>
<th>Mutagenic</th>
<th>Reproductive</th>
<th>Developmental</th>
<th>Endocrine Disruption</th>
<th>Neurological</th>
<th>Acute Toxicity</th>
<th>Systemic/Organ Effects</th>
<th>Sensitization (skin)</th>
<th>Irritation (respiratory)</th>
<th>Irritation (corrosion)</th>
<th>Corrosion (eyes)</th>
<th>Immune System Effects</th>
<th>Acute</th>
<th>Chronic</th>
<th>Persistence</th>
<th>Bioaccumulation</th>
</tr>
</thead>
</table>

**Ecotox. Fate**

- Low
- Moderate
- High
- Data Gap

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**The Green Screen for Safer Chemicals**

**VERSION 1.0**
GreenScreen®: Version 1.2

- Version 1.2 GreenScreen®
  - V. 1.2 changed endocrine endpoint from endocrine disruption to endocrine activity
  - >84% of v. 1.2 GreenScreens® have a data gap endocrine activity
GreenScreen®: Version 1.3

- Version 1.3 GreenScreen®
  - >76% of v. 1.3 GreenScreens® have a data gap endocrine activity

GreenScreen® Endocrine Activity Score (Version 1.3)

GreenScreen® for Safer Chemicals Hazard Assessment Guidance

V E R S I O N 1 . 3 • M A R C H 2 0 1 6
### GreenScreen®: Version 1.4

- **GreenScreen® v. 1.4**
- 76% of v 1.4 GreenScreens® have a data gap endocrine activity

#### GreenScreen® Endocrine Activity Score (Version 1.4)

<table>
<thead>
<tr>
<th>Endocrine Activity (E)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>[PERCENTAGE]</td>
</tr>
<tr>
<td>Moderate</td>
<td>[PERCENTAGE]</td>
</tr>
<tr>
<td>High</td>
<td>[PERCENTAGE]</td>
</tr>
<tr>
<td>Data Gap</td>
<td>[PERCENTAGE]</td>
</tr>
</tbody>
</table>

#### Table A1.5: Endocrine Activity (E)

<table>
<thead>
<tr>
<th>Information Type</th>
<th>Information Source</th>
<th>List Type</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Lists</td>
<td>EU - Priority Endocrine Disrupters</td>
<td>Screening</td>
<td>Category 3a</td>
</tr>
<tr>
<td></td>
<td>EU - SWHC Candidate List</td>
<td>Authoritative</td>
<td>Equivalent Concern - Candidate List; endocrine disrupting properties cause probable serious effects to the environment or human health</td>
</tr>
<tr>
<td></td>
<td>EU - SWHC Prioritisation List</td>
<td>Authoritative</td>
<td>Equivalent Concern - Prioritized for listing; endocrine disrupting properties cause probable serious effects to the environment or human health</td>
</tr>
<tr>
<td></td>
<td>EU - SWHC Authorisation List</td>
<td>Authoritative</td>
<td>Equivalent Concern - Authorized/Unless Authorized: endocrine disrupting properties cause probable serious effects to the environment or human health</td>
</tr>
<tr>
<td>B Lists</td>
<td>EU - Priority Endocrine Disrupters</td>
<td>Screening</td>
<td>Category 1 or 2</td>
</tr>
<tr>
<td></td>
<td>OSPAR</td>
<td>Authoritative</td>
<td>Endocrine Disruptor - chemical for priority action</td>
</tr>
<tr>
<td></td>
<td>OSPAR</td>
<td>Screening</td>
<td>Endocrine Disruptor - substance of possible concern</td>
</tr>
<tr>
<td></td>
<td>ChemSec - SIN List</td>
<td>Screening</td>
<td>Endocrine Disruption</td>
</tr>
<tr>
<td></td>
<td>TEDX - Potential Endocrine Disruptors</td>
<td>Screening</td>
<td>Potential Endocrine Disruptor</td>
</tr>
</tbody>
</table>
Impact of Criteria Change on Endocrine Activity Assessment

- More data gaps are filled (mostly by Moderate scores) with
  - Addition of authoritative/screening lists to this endpoint
  - Expansion of the evaluation from endocrine disruption to endocrine activity, and
  - Evaluation of plausibly related health effects from other human health endpoints

- From version 1.2 on, additional authoritative/screening lists did not significantly reduce the data gaps assigned to this endpoint.

- A Low score is almost never assigned due to insufficient data available to exclude activity in all endocrine pathways (i.e. estrogenic, anti-estrogenic, androgenic, antiandrogenic, and thyroid), unless the chemical is known to be not bioavailable.

- Overall, endocrine activity remains the most frequent data gap among all chemicals assessed, due to the lack of, or insufficient data.
Potassium permanganate (CAS #7722-64-7)

- Potassium permanganate is a GreenScreen® Benchmark 1
  - Moderate for endocrine activity based on altered sex hormones levels and advanced onset of puberty in humans and animals following exposure to manganese and its compounds (ATSDR 2012)
  
- Potentially plausibly related effects are insufficient to warrant modifying Endocrine Activity score

- Carcinogenicity-L – Do not modify score
- Developmental-H, but effects determined likely unrelated to EA – Do not modify score.
- Reproductive-M-potentially related to EA but score is M – Do not modify score.
- Systemic toxicity-vH and H, but unrelated to EA– Do not modify score.
Propylene glycol (CAS #57-55-6)

- Propylene glycol is a GreenScreen® Benchmark 3
  - A score of data gap for endocrine activity was assigned to Propylene glycol based on lack of sufficient data

- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors or the OSPAR List of Chemicals of Possible Concern.
  - Propylene glycol was active in:
    - 0/2 androgen receptor agonist and 0/13 androgen receptor antagonist assays
    - 0/26 estrogen receptor-alpha agonist and 0/1 estrogen receptor-alpha antagonist assays.
    - 0/6 thyroid receptor agonist and 0/14 thyroid receptor antagonist assays.
    - 0/5 thyroid stimulating hormone receptor agonist and 0/1 thyroid stimulating hormone receptor antagonist assay.
- No evidence of endocrine activity in data review

Despite robust search including HTS data, data are insufficient to assign a score for endocrine activity
Potassium acetate (CAS #127-08-2)

- Potassium acetate is a GreenScreen® Benchmark 2
  - A score of moderate for endocrine activity was assigned to potassium acetate based on thyroid effects in rats

- Increase in 131I intake, and TSH levels in 90-day oral study in rats with surrogate sodium acetate – Evidence of endocrine activity corresponds to M for Endocrine Activity endpoint
- No related effects for carcinogenicity, reproductive toxicity, or developmental toxicity (all assigned L) – Do not modify score
- Systemic toxicity – Effects not considered adverse or sufficient for GHS classification-assigned a L – Do not modify score

Moderate for Endocrine Activity based on evidence of endocrine activity without related effects drives the Benchmark score
Endocrine Activity Assessment—Recap of Examples

- Preliminary score of Moderate is rarely modified to a High as a result of related human health effects
  - Often there are no related human health effects
  - When there are related human health effects, hazard level is not always sufficient to trigger increase in preliminary score
  - Interesting note—when hazards for related human health effects are high enough to trigger increase in preliminary score, the Endocrine Activity score rarely drives the overall Benchmark score (i.e., a High for Group 1 human health endpoints already leads to a BM-1)

- Because Moderate requires only evidence of endocrine activity, this endpoint can sometimes drive the Benchmark score if there are no related human health effects

- Data gaps are common due to lack of sufficient data despite robust searches—data requirements are high and data are sparse
Among the GreenScreens® completed by ToxServices, more than 75% have a data gap, 17.3% have a moderate hazard, 1% have a high hazard, and 5.2% have a low hazard for endocrine activity.

Clients seem to be more concerned when a moderate hazard score is assigned for endocrine activity than when a data gap is assigned!
Resources: ToxFMD Screened Chemistry® Library

- All ToxServices Benchmark 1 GreenScreens® are posted for free!!
- Contact: Dr. Jen Tanir, jtanir@toxservices.com
- https://database.toxservices.com/