GreenScreen<sup>®</sup> Framework and Endocrine Activity: An Analysis of 1,000 GreenScreen<sup>®</sup> Assessments

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# **GreenScreen<sup>®</sup> Benchmark Scoring**

GreenScreen<sup>®</sup> 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





## **Endocrine Activity: Relation to GreenScreen® Benchmark Scores**

#### **Endocrine Activity hazard classification:**



## What Triggers Hazard Scores for Endocrine Activity in a GreenScreen<sup>®</sup> Assessment?

- GreenScreen<sup>®</sup> 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



### **Timeline of Endocrine-Related Criteria and GreenScreen®**

- GreenScreen<sup>®</sup>'s birthday is March 20, 2007
- GreenScreen<sup>®</sup> has undergone four major revisions (v. 1.0 − 1.4)



## **GreenScreen®: Version 1.0**

Low (L)

identified

No basis for concern

Moderate (M)

Analog data;

2; or Japanese list

Suggestive animal studies;

Chemical class known to produce toxicity:

EU Draft List - Category 1 or

Version 1.0 GreenScreen<sup>®</sup>

Very High (v)

Hazard

**Endocrine Disruption\*** 

High (H)

Endocrine disruption was one of the assessed hazard endpoints

Evidence of adverse effects in humans: or

of action lead to adverse effects

Weight of evidence demonstrates that mechanisms

>90% of v. 1.0 GreenScreens<sup>®</sup> had a data gap endocrine disruption

#### **GreenScreen<sup>®</sup> Endocrine Disruption**



|          |   |                |              |           |              |               | Hum                     | nan H        | ealth           | n Effe               | cts                  |                        |                        |                        |                    | Eco   | tox.    | Fa          | te              |
|----------|---|----------------|--------------|-----------|--------------|---------------|-------------------------|--------------|-----------------|----------------------|----------------------|------------------------|------------------------|------------------------|--------------------|-------|---------|-------------|-----------------|
|          |   | ion            |              | PI        | riorit       | y Eff         | ects                    |              |                 | cts                  |                      | atory)                 | skin)                  | (eyes)                 | cts                |       |         |             |                 |
| Chemical | Chemical<br>Abstract<br>Servies<br>Registry<br>Number<br>(CAS#) | % in Formulati | Carcinogenic | Mutagenic | Reproductive | Developmental | Endocrine<br>Disruption | Neurological | A cute Toxicity | Systemic/Organ Effec | Sensitization (skin) | Sensitization (respira | Irritation/Corrosion ( | Irritation/Corrosion ( | Immune System Effe | Acute | Chronic | Persistence | Bioaccumulation |

VERSION 1.0

THE GREEN SCREEN

FOR SAFER CHEMICALS

## **GreenScreen<sup>®</sup>: Version 1.2**

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

GREENSCREEN® CHEMICAL HAZARD ASSESSMENT PROCEDURE V1.2 Final Clean Production Action ©2013

GREENSCREEN® FOR SAFER CHEMICAL CHEMICAL HAZARD ASSESSMENT PROCEDURE



#### 🔲 Low 📃 Moderate 📕 High 🔲 Data Gap

|      |              | Information Type | Information Source | List Type                        | High (H)   | Moderate (M)                    | Low (L)   |
|------|--------------|------------------|--------------------|----------------------------------|--|---------------------------------|---|
| ЭC   | ш            | Data             | All Available Data |                                  | Evidence of endocrine activity and<br>related human health effect. | Evidence of endocrine activity. | Adequate data available, and negative<br>studies, and no structural alerts. |
| ÷E Č | $\mathbb{Z}$ |                  | EUED               | Screening                        |  |                                 | Category 3a   |
| SC   | 2            | A Lists          | EU SVHC            | Authoritative                    | Reason for Inclusion: Endocrine Activity                           |                                 |   |
| ŏ    | i≤. ∺        |                  | ELLED              | Screening                        | Category 1   | or 2                            |   |
| ŭ    | 히            |                  | EUED               | Screening                        |  | Category 3b                     |   |
| ш    | Ă١           | B Lists          | OSPAR              | Screening                        | Endocrine Dis  |                                 |   |
| _ `  |              |                  | SIN                | Screening                        | Reason for Inclusion: En   |                                 |   |
|      |              | TEDX             | Screening          | Listed on the TEDX List of Poter |  |                                 |   |

# **GreenScreen<sup>®</sup>: Version 1.3**

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

#### GreenScreen<sup>®</sup> Endocrine Activity Score (Version 1.3)

[PERCENTAGE]

[PERCENTAGE]

[PERCENTAGE]

CLEAN PRODUCTION ACTION

Information

GREENSCREEN VERSION 1.3 HAZARD CRITERIA 3



|            | .,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, |  | 2.00 .) p 0   |   |                                 |   |  |  |
|------------|---|--|---------------|---|---------------------------------|---|--|--|
| ty (E)     | Data                                    | All Available Data                               |               | Evidence of endocrine activity and related human health effect. | Evidence of endocrine activity. | Adequate data available, an negative studies, and no stralerts. |  |  |
| tivit      | A Lists                                 | EU – Priority Endocrine Disrupters               | Screening     |   |                                 | Category 3a   |  |  |
| e Act      |   | EU – SVHC Authorisation List                     | Authoritative | Equivalent Concern –<br>Candidate List                          |                                 |   |  |  |
| crin       | B Lists                                 | EU – Priority Endocrine Disrupters               | Screening     | Category 1 or 2   |                                 |   |  |  |
| <b>o</b> p |   |  |               | Category 3b   |                                 |   |  |  |
| <u>ل</u>   |   | OSPAR - Priority PBTs & EDs & equivalent concern | Screening     | Endocrine Disruptor   |                                 |   |  |  |
|            |   | ChemSec – SIN List                               | Screening     | Endocrine Disruption  |                                 |   |  |  |
|            |   | TEDX – Potential Endocrine Disruptors            | Screening     | Potential Endocrine Disruptor                                   |                                 |   |  |  |
|            |   |  |               |   |                                 |   |  |  |

## **GreenScreen®: Version 1.4**

- GreenScreen<sup>®</sup> v. 1.4
  - 76% of v 1.4 GreenScreens<sup>®</sup> have a data gap endocrine activity

TABLE A1.5: Endocrine Activity (E)

|                | Information<br>Type | Information Source                    | List Type     | High (H)   | Moderate (M)                   | Low (L)                                      |  |  |
|----------------|---------------------|---------------------------------------|---------------|--|--------------------------------|--|--|--|
|                | Data                | All Available Data                    |               | Evidence of endocrine activity and related human health effect   | Evidence of endocrine activity | Adequate data available and negative studies |  |  |
|                | A Lists             | EU – Priority Endocrine Disrupters    | Screening     |  |                                | Category 3a                                  |  |  |
|                |                     | EU – SVHC Candidate List              | Authoritative | Equivalent Concern - Candidate List: endocrine<br>disrupting properties cause probable serious<br>effects to the environment or human health               |                                |  |  |  |
| e Activity (E) |                     | EU - SVHC Prioritisation List         | Authoritative | Equivalent Concern – Prioritized for Listing:<br>endocrine disrupting properties cause prob-<br>able serious effects to the environment or<br>human health |                                |  |  |  |
| Endocrin       |                     | EU - SVHC Authorisation List          | Authoritative | Equivalent Concern – Banned Unless<br>Authorized: endocrine disrupting properties<br>cause probable serious effects to the<br>environment or human health  |                                |  |  |  |
|                | B Lists             | EU – Priority Endocrine Disrupters    | Screening     | Category 1 or 2  |                                |  |  |  |
|                |                     |                                       |               | Category 3b  |                                |  |  |  |
|                |                     | OSPAR                                 | Authoritative | Endocrine Disruptor - chemical for priority action   | n                              |  |  |  |
|                |                     | OSPAR                                 | Screening     | Endocrine Disruptor - substance of possible cond   |                                |  |  |  |
|                |                     | ChemSec - SIN List                    | Screening     | Endocrine Disruption   |                                |  |  |  |
|                |                     | TEDX - Potential Endocrine Disruptors | Screening     | Potential Endocrine Disruptor  |                                |  |  |  |

#### GreenScreen<sup>®</sup> Endocrine Activity Score (Version 1.4) [PERCENTAGE] [PERCENTAGE]

■ Low ■ Moderate ■ High ■ Data Gap

GreenScreen®

ar Chem

[PERCENTAGE]

VERSION 1.

[PERCENTAGE]

JANUARY 2018

### 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<sup>®</sup> 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)



- 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.

Potentially plausibly related effects are insufficient to warrant modifying Endocrine Activity score

# Propylene glycol (CAS #57-55-6)

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

| TOVSERVICES            |                     |                          |                           |                       |                        |                        |                |                    |     | G             | reenSc | reen®                                   | Score I   | nsp ec to       | r                             |   |   |   |                   |                            |              |   |
|------------------------|---------------------|--------------------------|---------------------------|-----------------------|------------------------|------------------------|----------------|--------------------|-----|---------------|--------|---|---|-----------------|-------------------------------|---|---|---|-------------------|----------------------------|--------------|---|
| 1.687                  | TONICOLOGY REK ASSE | SIMENT CONSULTING        | Table 1: I                | Hazard Ta             | ble                    |                        |                |                    |     |               |        |   |   |                 |                               |   |   |   |                   |                            |              |   |
|                        | Group I Human       |                          |                           |                       |                        | Group II and II* Human |                |                    |     |               |        |   |   |                 | Eco                           | cotox F   |   | ate Physical  |                   | sical                      |              |   |
|                        |                     | Ca reinogenicity         | Mutagenicity/Genotoxicity | Reproductive Toxicity | Developmental Toxicity | Endocrine Activity     | Acute Toxicity | Scretonic Toricity |     | Nanvotovicity |        | Skin Sensitization*                     | Respiratory Sensitization*  | Skin Irritation | Eye Irritation                | Acute Aquatic Toxicity                          | Chronic Aquatic Toxicity                    | Persistence   | Bioa ccumulatio n | Reactivity                 | Flammability |   |
| Table 2: Che           | mical Denil:        |                          |                           |                       |                        |                        |                |                    | S   | R*            | S      | R*                                      | *   | *               |                               |   |   |   |                   |                            |              |   |
| Inorganic<br>Chemical? | Chemical<br>Name    | CAS#                     | с                         | м                     | R                      | D                      | E              | AT                 | STS | STr           | Ns     | Nr                                      | SNS*  | SNR*            | IrS                           | IrE   | AA  | CA  | P                 | в                          | Rx           | F |
| No                     | Propyleue Glycol    | 57 <b>-</b> 55 <b>-6</b> | L                         | L                     | L                      | L                      | DG             | L                  | DG  | М             | м      | DG                                      | L   | L               | L                             | L   | L   | L   | vL                | vL                         | L            | L |
|                        |                     |                          | 7.11.1.1.1                | T                     |                        | ы.                     | 1              |                    |     |               |        |   | T-11- (   |                 | 1                             |   |   | 7-11-6  |                   | 1                          |              |   |
|                        |                     | Bencl                    | imark                     | a                     | b                      | c                      | d              | e                  | f   | b             |        | Table 4<br>Chemical Name<br>Beachmart 5 |   |                 | aiaary<br>creea©<br>ark Score | Table 6<br>aary<br>een ©<br>: Score<br>Progyle: |   | cal Name<br>Be uch mart Sco   |                   | asl<br>creea©<br>art Score |              |   |
|                        |                     |                          | 1<br>2                    | No<br>No              | No<br>No               | No<br>No               | No<br>No       | No<br>No           | No  | No            |        | Propylene Glycol                        |   | 3               |                               |   |   | Propylene Glycol  |                   | ol 3                       |              |   |
|                        |                     |                          | :                         | 3<br>4                | No<br>STOP             | No                     | Yes            | No                 |     |               |        |   | Note: Chemical has not undergene a data gap<br>assessment. Not a Final Gran Yer am <sup>The</sup> Score |                 |                               | ]   | After Data p<br>Note: No Da<br>GS Bench mar | s jap Americant<br>Data gap Americant Done if Preliming<br>mark Score is 1. |                   | nelim in ar y              |              |   |

- 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.
- High Throughput Screening (HTS) Data –PubChem (<u>http://pubchem.ncbi.nlm.nih.gov/</u>)
  - Propylene glycol was active in:
    - 0/2 and rogen receptor agonist and 0/13 and rogen 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<sup>®</sup> Benchmark 2
  - A score of moderate for endocrine activity was assigned to potassium acetate based on thyroid effects 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

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- 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 results 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

#### **Endocrine Activity Feedback and Areas of Disagreement**

- Among the GreenScreens<sup>®</sup> 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**

#### Resources: ToxFMD Screened Chemistry<sup>®</sup> Library

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

