Proposed Proposition 65
“No Significant Risk Level” (NSRL) for Glyphosate

Public Hearing on Rulemaking
Sacramento, California
June 7, 2017
Proposition 65

- The Safe Drinking Water and Toxic Enforcement Act of 1986
  - Adopted as a ballot proposition in 1986.
  - OEHHA maintains and updates a list of chemicals which cause cancer or reproductive toxicity.
    - Over 850 chemicals have been listed.
Specific requirements of Proposition 65

- Does not ban or restrict the use of a chemical.
- Applies to businesses with 10 or more employees – does not apply to governmental entities.
- Businesses must warn public of significant exposures.
- Businesses are prohibited from discharging significant amounts of listed chemicals to sources of drinking water.
- Attorney General, local prosecutors and private citizens can sue to enforce the law.
  - OEHHA does not have enforcement authority.
Proposition 65 listing of glyphosate

- OEHHA has determined glyphosate will be added to the Proposition 65 list of chemicals known to the state to cause cancer.
  - The date of the listing will be determined following a decision from the Court of Appeal on a request for a stay in the pending case *Monsanto v OEHHA*.
- Listing mechanism: California Labor Code Section 6382(b)(1)
  - The International Agency for Research on Cancer (IARC) classifies glyphosate in Group 2A (probably carcinogenic to humans), with *sufficient evidence* in animals.
Proposition 65 Safe Harbor Levels

- Are not limits on the use of a chemical.
- Are levels of exposure to listed chemicals that do not require a warning or trigger the discharge prohibition.
- Businesses use safe harbors as guidance by comparing them to exposure estimates.
  - Optional (business can prove different level should apply).
- Established using “evidence and standards of comparable scientific validity” to the basis for listing. (Title 27, CA Code of Regulations, Section 25701)
Safe Harbor Levels for carcinogens – No Significant Risk Levels (NSRLs)

- Regulations define the NSRL as the daily intake level calculated to result in one excess case of cancer in a population of 100,000 exposed individuals. (Section 25703)
NSRL development

Scientific analysis

OEHHA proposes NSRL, releases documents, publishes notice

45-day public comment period, public hearing upon request

OEHHA considers comments

No substantive changes made

OEHHA responds to comments and submits final regulation to the Office of Administrative Law

Substantive changes made

OEHHA makes changes and publishes notice

15-day public comment period
Scientific analysis for NSRL development

- Dose-response assessment: Determining a chemical’s likelihood of causing cancer depending on the dose received.

- Exposure assessment (determining the actual level of exposure from a product or activity) is not part of the NSRL development process.
  - Exposure assessments for specific exposures are done by businesses causing the exposure, and others.
  - The estimated levels of exposure are compared to the NSRL to determine if a warning is required.
Scientific process for developing an NSRL

- **Cancer potency estimation**
  - A chemical’s cancer potency estimate is an independent measure of a chemical’s ability to cause cancer.

- **Risk-specific intake level calculation**
  - Daily intake of a chemical to enter the body to pose a lifetime risk of cancer of 1 in 100,000 (NSRL)
Cancer potency estimation for glyphosate

- Based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing.
- Listing based on IARC (2015) carcinogenicity evaluation
  - Limited evidence in humans.
  - **Sufficient evidence in experimental animals.**
- Strong evidence that glyphosate has two key characteristics of known human carcinogens:
  - Genotoxicity (the ability to cause mutations and other DNA damage that can lead to cancer), based on human and animal studies.
  - Oxidative stress (an imbalance in cellular oxidation status; can result in oxidative damage to DNA and genomic instability that can lead to cancer), based on human and animal studies.
Study selection for cancer potency estimation for glyphosate

- Reviewed the animal studies discussed by IARC (2015)
- Most sensitive study of sufficient quality:
  - Two-year diet study conducted in male CD-1 mice
    - Performed by Inveresk Research International

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Dose group (mg/kg-day)</th>
<th>Exact trend test p-value</th>
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<tbody>
<tr>
<td>Hemangiosarcoma</td>
<td>0/50 0/50 0/50 4/50</td>
<td>p = 0.0036</td>
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Model approach to cancer potency estimation for glyphosate

- “Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans.” (IARC, 2015)
- The multistage polynomial model for cancer in US EPA’s Benchmark Dose Software was applied to derive a cancer potency estimate.
- Interspecies scaling was done to take into account body size differences between humans and experimental animals.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Animal cancer potency [(mg/kg-day)^-1]</th>
<th>Human cancer potency [(mg/kg-day)^-1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangiosarcoma</td>
<td>0.000000897</td>
<td>0.00062</td>
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</table>
Risk-specific intake level calculation: Glyphosate NSRL

\[
\text{NSRL} = \frac{10^{-5} \times 70 \text{kg}}{\text{cancer potency}} \times 1000 \mu\text{g/mg}
\]

- **Cancer Potency**: 0.00062 (mg/kg-day)^{-1}
- **Daily intake posing 1 in 100,000 lifetime risk of cancer (NSRL)**: 1100 micrograms per day
- **This number is compared to estimated exposures to determine if warnings are required.**