

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

Public Hearing on Rulemaking  
Sacramento, California  
June 7, 2017



**OEHHHA**  
SCIENCE FOR A HEALTHY CALIFORNIA

# 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

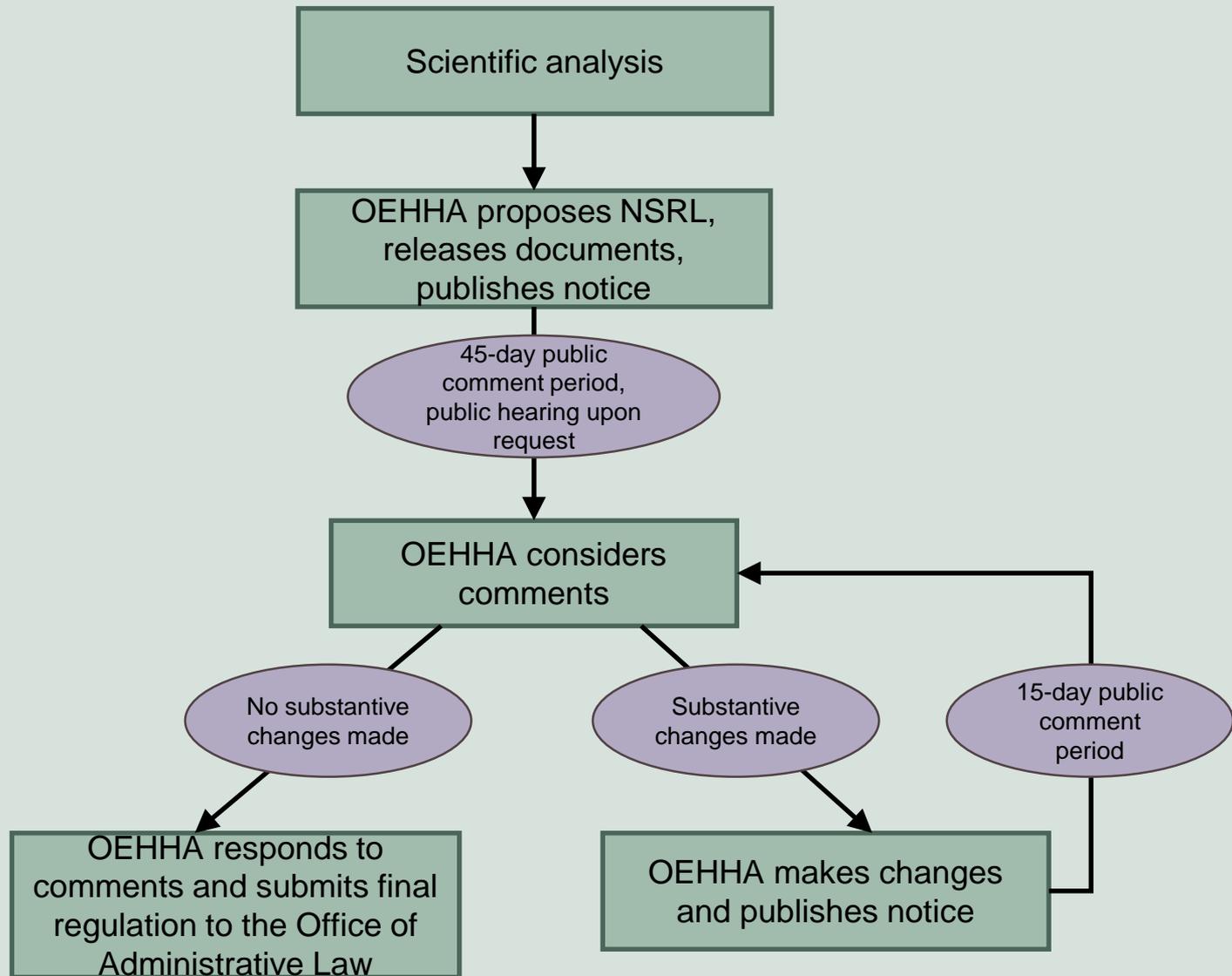
- Are not limits on the use of a chemical.
- Are levels of exposure to listed chemicals that do not require a warning or trigger the discharge prohibition.
- Businesses use safe harbors as guidance by comparing them to exposure estimates.
  - Optional (business can prove different level should apply).
- 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)

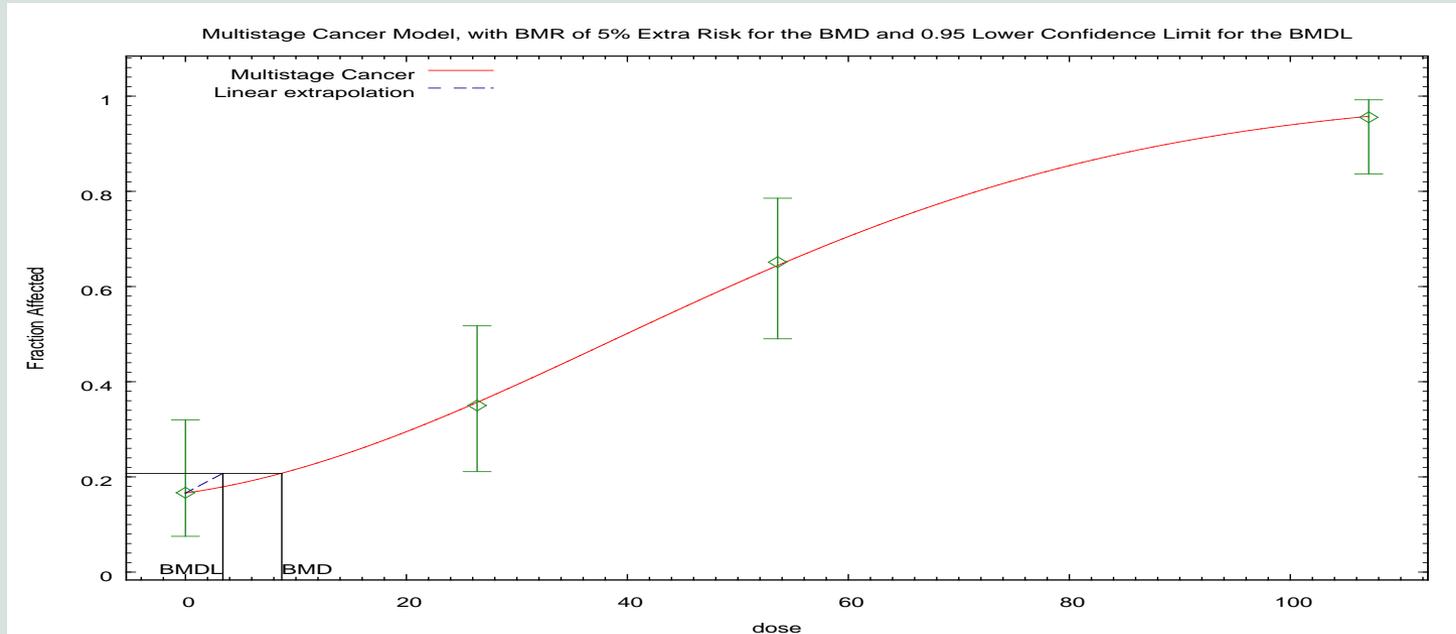
- Regulations define the NSRL as the daily intake level calculated to result in one excess case of cancer in a population of 100,000 exposed individuals. (Section 25703)

# NSRL development



# Scientific analysis 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
    - Summarized by IARC (2015) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2006).

Tumor type	Dose group (mg/kg-day)				Exact trend test p-value
	0	100	300	1000	
Hemangiosarcoma	0/50	0/50	0/50	4/50	p = 0.0036



# 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.

Tumor type	Animal cancer potency [(mg/kg-day) <sup>-1</sup> ]	Human cancer potency [(mg/kg-day) <sup>-1</sup> ]
Hemangiosarcoma	0.00000897	0.00062



# Risk-specific intake level calculation: Glyphosate NSRL

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

- **Cancer Potency:**  $0.00062 \text{ (mg/kg-day)}^{-1}$
- **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.

