Proposed Public Health Goal for 1,4-Dioxane in Drinking Water

Public Workshop

November 13, 2025

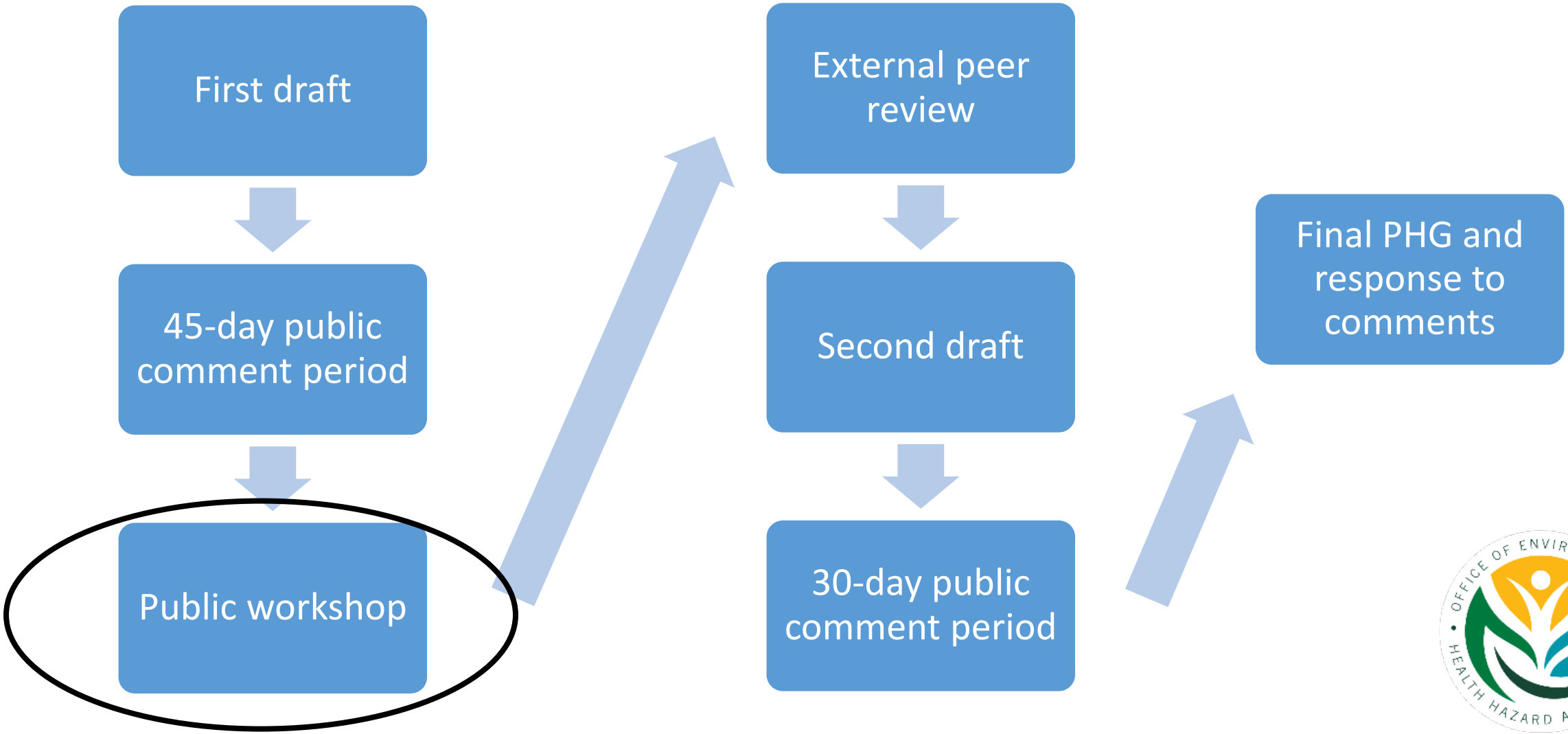
Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

PHG Program Background

- A Public Health Goal (PHG) is the level of a chemical contaminant in drinking water that does not pose a significant risk to health over a lifetime
  - Analogous to US EPA's Maximum Contaminant Level Goals (MCLGs)
- For carcinogens, OEHHA derives health-protective concentrations (HPCs) based on both cancer and noncancer effects; the lower of the two is chosen as the PHG
- The Calderon-Sher Safe Drinking Water Act of 1996 requires the State Water Resources Control Board (SWRCB) to set Maximum Contaminant Levels (MCLs) as close to the corresponding PHG as is economically and technologically feasible

Public Health Goal Process



Outline of Presentation

- Background of 1,4-dioxane
- Derivation of the noncancer based HPC
- Derivation of the cancer based HPC
- Next Steps

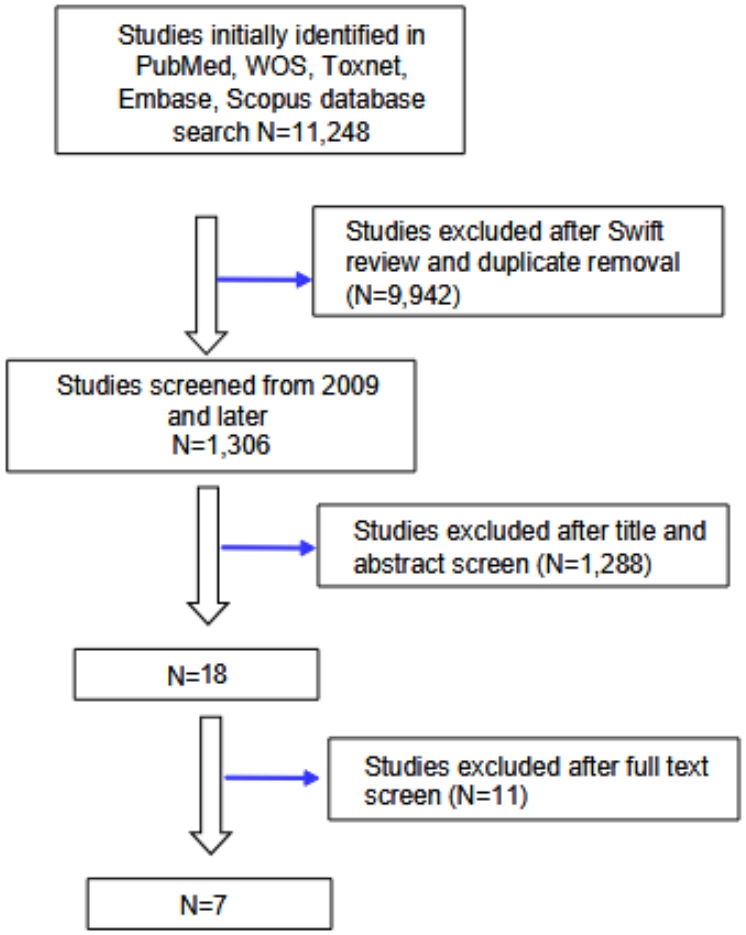
1,4-Dioxane

- Used as a solvent in industrial applications, e.g., wetting and dispersing agent, degreasing agent, component in various paints.
- 1,4-dioxane is released into the environment through industrial and commercial production and use of consumer products.
- Humans can be exposed to 1,4-dioxane through sources such as air, soil, food, and consumer and industrial products, in addition to drinking water.

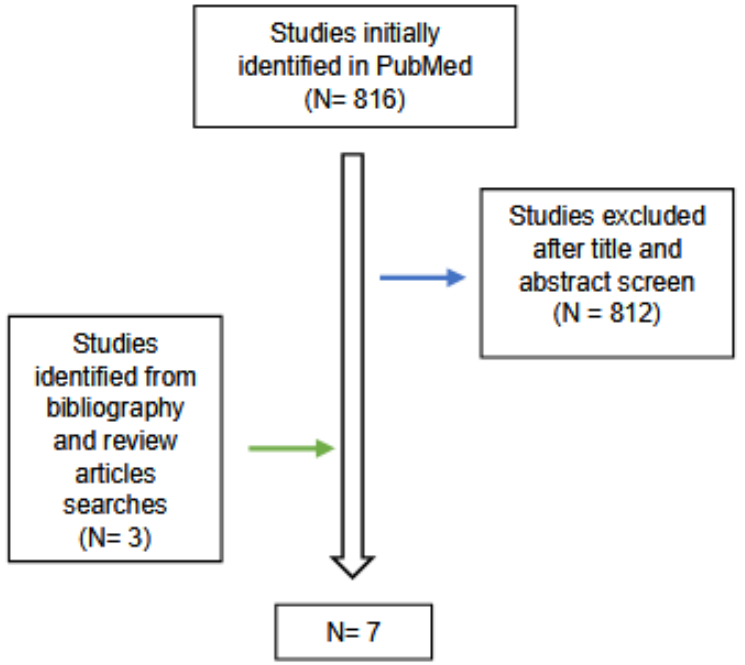
Notification Level

- In 1998, the Drinking Water Program at the California Department of Public Health established a notification level (NL) of 3 parts per billion (ppb).
- NLs are health based advisory levels established by SWRCB for certain chemicals without MCLs, and when exceeded prompt certain requirements and recommendations.
- In 2010, the NL was revised to 1 ppb when US EPA concluded that a one-in-a-million risk would correspond to a concentration of 0.35 ppb.
- In 2019, SWRCB requested that OEHHA develop a PHG which will be used to establish an MCL.

Literature Search Strategy



A. General search of human, animal and in vitro studies



B. Search of human epidemiology studies only

Derivation of Noncancer Based HPC

Point of Departure (POD)

- No candidate human epidemiologic studies were considered suitable to assess dose-response relationships for 1,4-dioxane and noncancer outcomes
- Critical study – Kociba et al. (1974)
  - Administered 1,4-dioxane to male and female rats in drinking water for 2 years
- Critical endpoint – histopathological changes in the kidney and liver of male rats
- The data were not amenable to benchmark dose (BMD) modeling
- No-Observed-Adverse-Effect Level (NOAEL): 9.6 milligrams/kilogram body weight per day (mg/kg-day)

Acceptable Daily Dose (ADD)

$$\text{ADD} = \text{POD} \div \text{combined UF}$$

Uncertainty Factors (UFs)

- Interspecies (UF_A): 10
- Intraspecies toxicokinetics ($UF_{H\text{-}k}$): √10
- Intraspecies toxicodynamics ($UF_{H\text{-}d}$): 10
- Database deficiencies (UF_D): √10
- Combined UF: 1,000

$$ADD = 9.6\, mg/kg - day \div\ 1{,}000\ = 0.0096\, mg/kg - day$$

Calculation of the Noncancer HPC

HPC = ADD × RSC ÷ DWI

where:

ADD = acceptable daily dose of 0.0096 mg/kg-day

RSC = relative source contribution of 0.2

DWI = daily water intake of 0.059 L_{eq}/kg-day

HPC = 0.0096 mg/kg-day × 0.2 ÷ 0.059 L_{eq}/kg-day = 0.033 mg/L or 33 ppb (rounded)

The HPC for noncancer effects is 33 ppb.

Derivation of Cancer Based HPC

Cancer HPC Derivation

$$HPC = \frac{R}{[(CSF_{oral} \times DWI_{lifetime}^{oral}) + (CSF_{inh} \times DWI_{lifetime}^{inh})]}$$

where:

R = default risk level of one in one million, or 10^{-6}

CSF_{oral} = oral cancer slope factor, in $(mg/kg\text{-}day)^{-1}$

CSF_{inh} = inhalation cancer slope factor, in $(mg/kg\text{-}day)^{-1}$

$DWI_{lifetime}^{inh/oral}$ = total lifetime daily exposure for inhalation or oral

Critical Study Selection

- No candidate human epidemiologic studies were considered suitable to assess dose-response relationships for 1,4-dioxane and cancer outcomes
- Selected Kano et al. (2009) and JBRC (1998) studies as the critical studies of oral exposure and Kasai et al. (2009) as the critical study for inhalation exposure
  - Most sensitive studies
  - Chronic duration
  - Drinking water for oral exposure
  - Vapor for inhalation exposure
  - Multiple doses/concentrations
  - Large sample size

Dose-Response Assessment (Oral)

- Rats
  - Statistically significant increases in nasal tumors, hepatocellular adenomas or carcinomas, mammary gland tumors, subcutis fibroma and mesothelioma of the peritoneum in males.
  - Statistically significant increases in nasal tumors, hepatocellular adenoma or carcinoma, and mammary gland tumors in females.
- Mice
  - Hepatocellular adenomas and carcinomas and hemangioendothelioma of the heart in males.
  - Hepatocellular adenomas and carcinomas in females.
- BMDS Multi-site Cancer analysis was used for the male rat, female rat and male mouse datasets. BMDS Multi-stage Weibull model was used for the female mouse dataset due to significant treatment-related mortality.

Mechanistic Considerations

- Multiple mechanisms for carcinogenesis
  - cytotoxicity
  - oxidative stress
  - genotoxicity
  - cell proliferation
  - chronic inflammation
  - increased cell proliferation
- Evidence for a singular predominant mechanism for carcinogenesis is not conclusive

➢Default linear low-dose extrapolation used for dose-response analysis

Calculation of Animal Oral Cancer Slope Factor (CSF)

	Male Rats	Female Rats	Male Mice	Female Mice
Tumors	Nasal cavity tumors, hepatocellular adenoma or carcinoma, mammary gland tumors, subcutis fibroma, and peritoneal mesothelioma	Nasal cavity tumors, hepatocellular adenoma or carcinoma, and mammary gland tumors	Hepatocellular adenoma or carcinoma and hemangioendothe-lioma of the heart	Hepatocellular adenoma or carcinoma
BMDL (mg/kg-day)	5.54	22.88	7.11	1.85
CSF_{animal} $(mg/kg\text{-}day)^{-1}$	0.0090	0.0022	0.0070	**0.027**

CSF – Animal to Human Conversion

$$\text{Human CSF}_{oral} = \text{Animal CSF}_{oral} \times (\text{body weight}_{human} \div \text{body weight}_{animal})^{1/4}$$

$$= 0.027\ (\text{mg/kg-day})^{-1} \times (70\ \text{kg} \div 0.0353\ \text{kg})^{1/4}$$

$$= 0.18\ (\text{mg/kg-day})^{-1}$$

Age Sensitivity Factors (Oral)

OEHHA applies Age Sensitivity Factors (ASFs) to account for increased susceptibility of infants and children to carcinogens.

Stage	Age Sensitivity Factor (ASF)[a]	Fractional Duration [b] (d)	Daily Water Intake (DWI, L/kg-day)	ASF × d × DWI (L/kg-day)
3rd trimester (Pregnancy)	10	0.25/70	0.047	0.0017
Infant (0-2 yr)	10	2/70	0.196	0.0560
Child (2-16 yr)	3	14/70	0.061	0.0366
Adult (16-70 yr)	1	54/70	0.045	0.0347
			Total Lifetime Exposure	0.1290

$DWI_{lifetime}^{oral} = 0.1290\ L_{eq}/kg\text{-}day$

Dose-Response Assessment (Inhalation)

- Male rats
  - Statistically significant increases in nasal cavity squamous cell carcinoma, hepatocellular adenoma or carcinoma, peritoneal mesothelioma, mammary gland fibroadenoma, zymbal gland adenoma, renal cell carcinoma, and subcutis fibroma
- BMDS Multi-site Cancer analysis was used

➢Default linear low-dose extrapolation used for dose-response analysis

Calculation of Inhalation CSFs

	Male Rats
Tumors	Nasal cavity squamous cell carcinoma, hepatocellular adenoma or carcinoma, peritoneal mesothelioma, mammary gland fibroadenoma, zymbal gland adenoma, renal cell carcinoma, subcutis fibroma
BMDL (mg/kg-day)	9.17
CSF_{animal} $(mg/kg\text{-}day)^{-1}$	0.00545
CSF_{human} $(mg/kg\text{-}day)^{-1}$	0.020

Age Sensitivity Factors (Inhalation)

Stage	Age Sensitivity Factor (ASF)[a]	Fractional Duration[b] (d)	Daily Water Intake (DWI, L_{eq}/kg-day)	ASF × d × DWI (L_{eq}/kg-day)
3rd trimester (Pregnancy)	10	0.25/70	0.006	0.0002
Infant (0-2 yr)	10	2/70	0[c]	0.0000
Child (2-16 yr)	3	14/70	0.012	0.0072
Adult (16-70 yr)	1	54/70	0.004	0.0031
			Total Lifetime Exposure	0.0105

$DWI_{lifetime}^{inh}$ = 0.0105 Leq/kg-day

Calculation of the Cancer HPC

$$HPC = \frac{R}{(CSF_{oral} \times DWI_{lifetime}^{oral}) + (CSF_{inh} \times DWI_{lifetime}^{inh})}$$

$$HPC = \frac{10^{-6}}{(0.18\ (mg/kg\text{-}day)^{-1} \times 0.1290\ Leq/kg\text{-}day) + (0.02\ (mg/kg\text{-}day)^{-1} \times 0.0105\ Leq/kg\text{-}day)}$$

$$= 0.000043\ mg/L = 0.04\ \mu g/L \text{ or ppb (rounded)}$$

The HPC for cancer effects is 0.04 ppb.

Proposed Noncancer and Cancer HPCs

- Noncancer
  - Liver and kidney toxicity from the Kociba et al. (1974) study
  - Use of lifetime weighted average drinking water intake rates and uncertainty factors
  - ➢Proposed HPC: 33 ppb
- Cancer
  - Liver tumors from Kano et al. (2009) and JBRC (1998) for oral
  - Multiple tumor types from Kasai et al. (2009) for inhalation
  - Benchmark dose modeling
  - Use of lifetime weighted average drinking water intake rates and age sensitivity factors
  - ➢Proposed HPC: 0.04 ppb

➢Proposed PHG: 0.04 ppb

Next Step: External Scientific Peer Review

- Mediated by External Scientific Peer Review Program at the State Water Resources Control Board
- Request for experts in:
  - Risk Assessment
  - Cancer toxicology
  - Mammalian toxicology
  - Environmental epidemiology
- Critical issues for peer reviewers:
  - Critical study and endpoint selection
  - Cancer evaluation and mode of action
  - Epidemiology conclusions

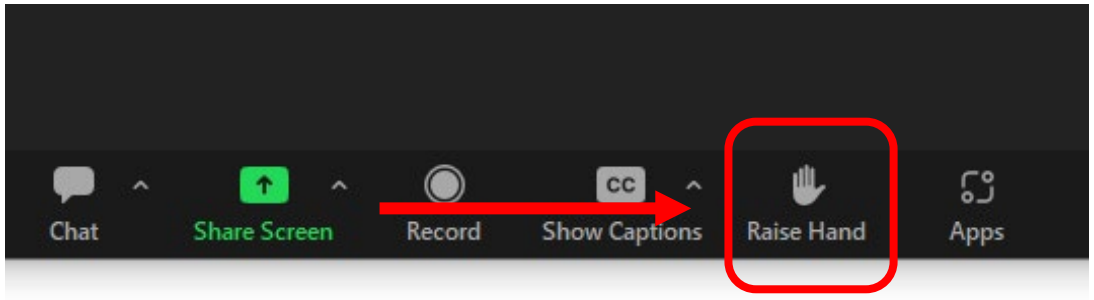
Clarifying Questions

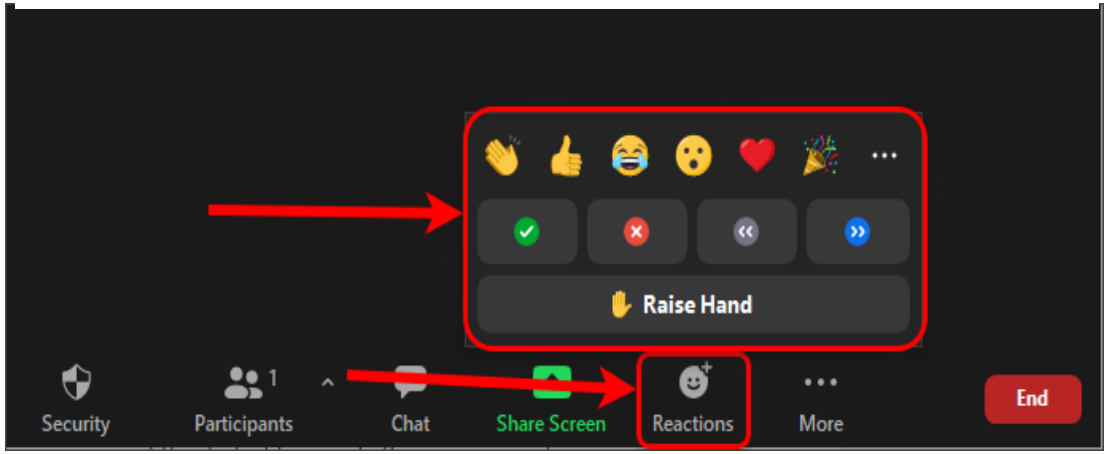
How to ask a question

1. In person – When called on, please come to the podium to ask your question.

2. Online via Zoom – When requested, raise your virtual hand. You will be called on and unmuted. The raise hand feature may be an icon that says, “raise hand” or it may be one of the **options** under, “reactions.”

Zoom webinar
Raise hand feature





Public Comments

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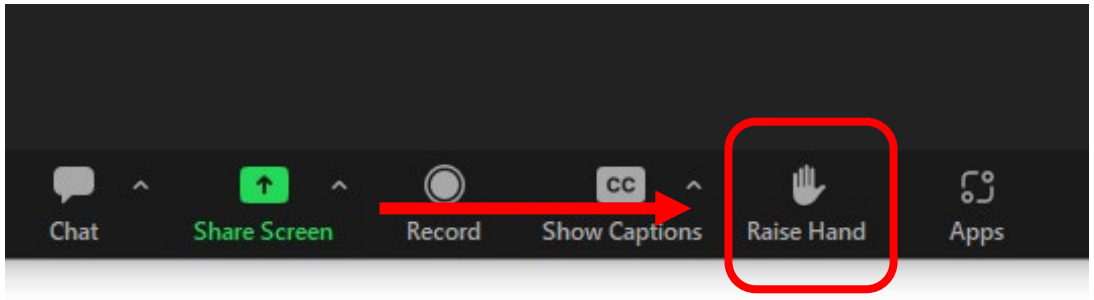

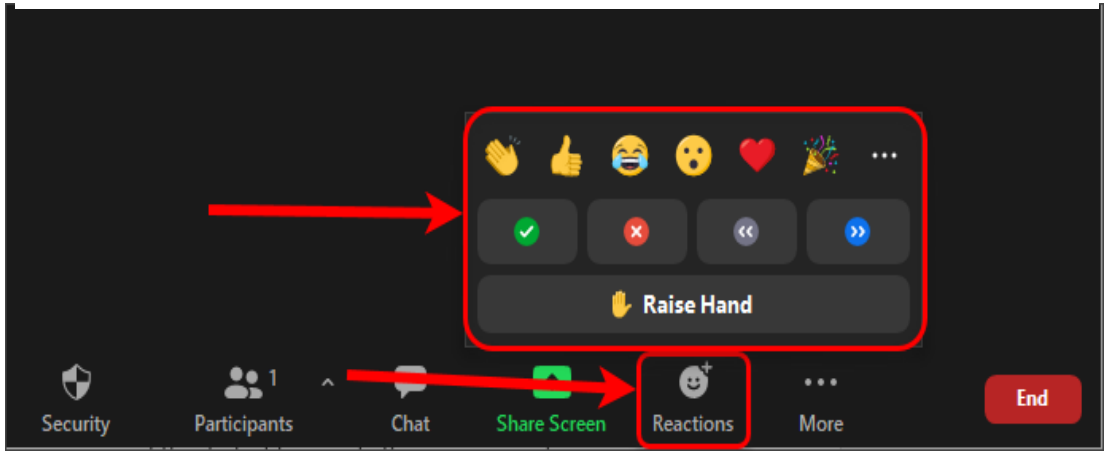

Next Steps

- The public comment period is open until November 25, 2025

https://oehha.ca.gov/comments

- The first draft will receive independent, external peer review
- The second draft will address peer-review and public comments, followed by further opportunity for public comment
- Final document includes response to public and peer review comments