Proposition 65

Initial Statement of Reasons

Title 27, California Code of Regulations

Proposed Amendments to Article 6:

Safe Harbor Clear and Reasonable Warnings for Acrylamide Exposures from Food

New subsection 25607.2(b)

September 24, 2021

California Environmental Protection Agency

Office of Environmental Health Hazard Assessment

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I. Summary

Proposition 65[1] requires businesses to provide a clear and reasonable warning before they knowingly and intentionally cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity.[2] The Office of Environmental Health Hazard Assessment (OEHHA) is the lead agency that implements Proposition 65[3] and has the authority to promulgate and amend regulations to implement and further the purposes of the Act. OEHHA is proposing to adopt a new safe harbor warning regulation to provide more specific and descriptive language for warnings for exposure to acrylamide from food.

This proposed rulemaking would add a subsection to OEHHA's regulations in Title 27, California Code of Regs., section 25607.2[4], that provide warning content for exposures to Proposition 65 listed chemicals in food. This proposed regulation would add an additional non-mandatory, safe harbor warning option for businesses that cause significant exposures to acrylamide from food[5]. Compliance with the regulation by businesses will reduce the potential for litigation concerning the sufficiency of warnings because the content and methods provided in the safe harbor regulations[6] are deemed "clear and reasonable" by the lead agency for purposes of the Act. The content of the proposed warning is also intended to provide information to individuals who may be exposed to acrylamide in food that can help them make better informed decisions about those exposures.

II. Background/Problem to be Addressed by the Proposed Rulemaking

Food subject to warnings for acrylamide exposures

In August 2020, OEHHA began a rulemaking to adopt a regulation addressing exposures to listed chemicals in foods created by cooking or heat processing. When completed the regulation will establish specific levels deemed to be the lowest level currently feasible for specific categories of foods. The regulation would adopt such levels for acrylamide. Once the rulemaking is adopted, fewer foods will need a warning

[1] Health and Safety Code section 25249.5 et seq., The Safe Drinking Water and Toxic Enforcement Act of 1986, commonly known as "Proposition 65". Hereafter referred to as "Proposition 65" or "the Act".
[2] Health and Safety Code section 25249.6.
[3] The Safe Drinking Water and Toxics Enforcement Act of 1986, codified at Health and Safety Code Section 25249.5 et seq., commonly known as Proposition 65, herein referred to as the "Act" or "Proposition 65".
[4] All references are to sections of Title 27, California Code of Regulations, unless otherwise indicated.
[5] For carcinogens, a warning is not required when the person responsible can show the exposure poses no significant risk assuming lifetime exposure at the level in question (Health and Safety Code Section 25249.10). OEHHA adopted a No Significant Risk Level (NSRL) of 0.2 micrograms per day in Title 27, Cal. Code of Regs., section 25705. Exposures below this safe harbor level do not require warning.
[6] Title 27, California Code of Regs., section 25601 et seq.

under Proposition 65, but some with high levels of exposure will still need warnings. Therefore, a specific safe harbor warning for these exposures is warranted.

OEHHA is also aware of the federal District Court decision in the *California Chamber of Commerce v Bonta* (CalChamber) case in which the California Chamber of Commerce challenged the existing safe harbor Proposition 65 warning as applied to acrylamide in food, arguing that such warnings are false and misleading and therefore, a violation of the First Amendment rights of its members.[7] The District Court issued a preliminary injunction against the filing of new enforcement actions after March 29, 2021. The merits of that case will likely be heard in the District Court in Summer 2022. While the District Court enjoined the filing of new enforcement actions, businesses were not enjoined from providing a warning if they choose to do so. An intervenor in the case filed an appeal in the Ninth Circuit Court of Appeals, challenging entry of the preliminary injunction. The Ninth Circuit stayed the preliminary injunction to the extent it bars private enforcers from prosecuting actions enforcing Proposition 65's warning as applied to acrylamide.[8]

OEHHA's safe harbor regulations are non-mandatory guidance. OEHHA does not have enforcement authority under Proposition 65 and thus cannot enforce the Proposition 65 warning requirement for an exposure to any listed chemical, including acrylamide. The preliminary injunction in the CalChamber case, however, is still in effect as to enforcement actions brought by public prosecutors. Therefore, new enforcement actions can be brought by private enforcers against businesses.

OEHHA has considered the concerns expressed in the District Court's preliminary injunction order in developing the proposed regulation. The purpose of the proposed regulation is to provide an additional optional safe harbor warning for businesses that addresses the District Court's concerns as well as public health concerns.

The proposed warning would be adopted into the safe harbor regulations for foods which identify warnings specifically determined to be "clear and reasonable" for purposes of Proposition 65. It provides important information for consumers and protection for business who choose to use it.

Public health concern for acrylamide cancer risks from food consumption

Acrylamide is a chemical that is formed in certain plant-based foods during cooking or processing at high temperatures, such as frying, roasting, grilling, and baking. It was originally added to the Proposition 65 list of chemicals in 1990 as known to cause

[7] Eastern District of California, Case No. 2:19-CV-02019-KJM-EFB.
[8] Ninth Circuit Court of Appeals, Case No. 21-15745.

cancer, based on a finding by the US Environmental Protection Agency (US EPA) that acrylamide is a "probable human carcinogen."[9]

In August 2002, scientists at Stockholm University published findings that acrylamide is created in certain foods when they are cooked, or heat processed at high temperatures.[10] Shortly thereafter, enforcement actions for failure to warn about acrylamide exposures from foods began to be filed. Enforcement action by private parties under Proposition 65 begins with service of a notice of violation on the business, Attorney General, and other prosecutors. More than 1,200 such notices have been filed in California regarding unwarned exposures to acrylamide from a variety of food including French fries, potato chips, breads, cereals, and coffee.[11]

There is no serious scientific debate about the carcinogenicity of acrylamide, or its potential for carcinogenicity in humans. There is extensive evidence of carcinogenicity from studies in animals and detailed mechanistic studies of human and animals. Acrylamide is unequivocally a carcinogen in animals that causes tumors in multiple sites in rats and mice of both sexes. An overview of the available experimental data is provided in Appendix A.

Based on this extensive evidence of carcinogenicity, several prominent authorities have described the potential for acrylamide to be a human carcinogen as follows:

- The International Agency for Research on Cancer (IARC):
  - probably carcinogenic to humans[12]
- The National Toxicology Program (NTP). NTP Report on Carcinogens (RoC):
  - reasonably anticipated to be a human carcinogen[13]
- US Environmental Protection Agency (US EPA):
  - likely to be carcinogenic to humans[14]
- National Institute of Occupational Safety and Health (NIOSH):
  - potential occupational carcinogen

[9] National Service Center for Environmental Publications, *Acrylamide 79-06-1* (Sept. 8, 2021) https://nepis.epa.gov/Exe/ZyPDF.cgi/P100ZKZT.PDF?Dockey=P100ZKZT.PDF
[10] Tareke E, Rydberg P, Karlsson P, Eriksson S, Törnqvist M, *Analysis of Acrylamide, A Carcinogen Formed in Heated Foodstuffs,* Journal of Agricultural and Food Chemistry (Aug. 14, 2002) National Library of Medicine, https://pubmed.ncbi.nlm.nih.gov/12166997/ (Sept. 8. 2021)
[11] Information available from California State Attorney General data on Proposition 65 Enforcement Reporting. (Sept. 7, 2021) https://oag.ca.gov/prop65
[12] https://publications.iarc.fr/78 and https://monographs.iarc.who.int/list-of-classifications.
[13] https://ntp.niehs.nih.gov/ntp/roc/content/profiles/acrylamide.pdf
[14] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0286tr.pdf

- European Food Safety Agency (EFSA):
  - Acrylamide exposure "can potentially increase the risk of developing cancer for consumers in all age groups"[15]

Because of concerns over the potential carcinogenic risks to humans from consuming foods with acrylamide, several governmental organizations have called for or are recommending ways to reduce formation of acrylamide in food and human exposures to it through consumption of food.

- The US Food and Drug Administration issued:
  - *Guidance for Industry: Acrylamide in Foods* "to help growers, manufacturers, and food service operators reduce acrylamide levels in certain foods."[16,17]
  - Guidance to consumers: *You Can Help Cut Acrylamide in Your Diet*[18], and "other resources that contain information about acrylamide and ways to reduce exposure from foods prepared at home."[19]
- The European Union adopted:
  - A regulation, in 2017, establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in food.[20]
- The United Nation's Joint FAO (Food and Agriculture Organization of the United Nations)/WHO (World Health Organization) Expert Committee on Food Additives (JECFA)[21] recommended that:
  - "work to reduce exposure to acrylamide in food by minimizing its concentrations should continue."
  - "information on the occurrence of acrylamide in food consumed in developing countries would be useful to conduct a dietary exposure assessment and consider appropriate mitigation strategies to minimize acrylamide concentrations in food."

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[15] https://www.efsa.europa.eu/en/topics/topic/acrylamide
[16] https://www.fda.gov/food/cfsan-constituent-updates/fda-issues-final-guidance-industry-how-reduce-acrylamide-certain-foods
[17] FDA, Guidance for Industry: Acrylamide in Foods, US DHHS, FDA, Center for Food Safety and Applied Nutrition, March 2016. Available at: https://www.fda.gov/media/87150/download
[18] https://www.fda.gov/consumers/consumer-updates/you-can-help-cut-acrylamide-your-diet
[19] https://www.fda.gov/food/chemical-contaminants-food/acrylamide
[20] Official Journal of the European Union. Commission Regulation (EU) 2017/2158
[21] JECFA, Evaluation of Certain Contaminants in Food, Seventy-second report, WHO Technical Report Series No. 959, page 9. Available at; http://apps.who.int/iris/bitstream/handle/10665/44514/WHO_TRS_959_eng.pdf;jsessionid=1534D51FDA74049BA4DE24B406A3EB38?sequence=1

- FAO/WHO Codex Alimentarius issued:
    - Code of Practice for the Reduction of Acrylamide in Foods" (CAC/RCP 67-2009) "to provide national and local authorities, manufacturers and other relevant bodies with guidance to prevent and reduce formation of acrylamide in potato products and cereal products."

These public health concerns underscore the importance of providing Proposition 65 warnings prior to significant exposures to acrylamide in food and indicate a need for a more specific and informative Proposition 65 warning for these exposures.

Although acrylamide was listed in 2011 under Proposition 65 as a reproductive toxicant because of NTP findings of adverse effects on developmental and the male reproductive system[22], exposures through food sufficiently high to trigger the warning requirement are highly unlikely and so the regulatory proposal only covers the cancer endpoint.

III. Proposed amendment: Specific warning language for acrylamide exposure from food

OEHHA is proposing to amend the warning regulations for food exposures in section 25607.2, by adding subsection 25607.2(b) to provide optional, more specific warning content for acrylamide exposures from food. Currently, businesses can use the general food warning content found in subsection 25607.2(a). Both subsections (a) and (b) are completely voluntary alternatives for providing safe harbor warnings and both use the methods in Section 25607.1. A business may provide a warning using one of these provisions, or it may provide a warning using any other language it deems "clear and reasonable" as required by the Act. However, if a business chooses to use other warning content or methods, it may need to defend those choices in the event an enforcement action is filed against it.

The proposed amendment would not alter subsection (a).[23] Thus, a business that already uses warning language set forth in subsection (a) need not alter existing warnings for its products, because the warning it provides will continue to be deemed "clear and reasonable" as required by the Act.

There are two components to the warning content that are required in the alternative subsection (b) warning. These provide as follows:

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[22] NTP (2005). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide. NIH Publication No. 05-4472. US Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. Available from: https://ntp.niehs.nih.gov/ntp/ohat/acrylamide/acrylamide_monograph.pdf

[23] The warning set forth in subsection (a) as applied to acrylamide would read: "WARNING: Consuming this product can expose you to chemicals including acrylamide, which is known to the State of California to cause cancer. For more information go to www.P65Warnings.ca.gov/food."

In proposed subsection (b)(1), to make it clear that the warning is being given under a California law, the warning begins with words “CALIFORNIA WARNING” in all capital letters and bold print for easy identification.

Proposed new subsection (b)(2) provides the acrylamide specific warning language as follows:

> “Consuming this product can expose you to acrylamide, a probable human carcinogen formed in some foods during cooking or processing at high temperatures. Many factors affect your cancer risk, including the frequency and amount of the chemical consumed. For more information including ways to reduce your exposure, see www.P65Warnings.ca.gov/acrylamide.”

The proposed warning language includes several elements to improve the usefulness and informativeness of the warning for the consumer. The proposed regulation:

- explains that the person must consume the product to be exposed to acrylamide.
- provides the description that acrylamide is “a probable human carcinogen” for context. As discussed above, this language is consistent with the findings of the authoritative entities that have evaluated the carcinogenicity of acrylamide. Specifically, there are a number of different but very similar narrative statements used by authoritative entities to describe the potential for acrylamide exposure to cause human cancer. In 1990, when acrylamide was added to the Proposition 65 list the US EPA used the terminology “probable human carcinogen” with respect to acrylamide.[24] In 2010 when US EPA re-evaluated acrylamide it used the new term adopted in its 2005 Carcinogen Risk Assessment Guidelines[25] “likely to be carcinogenic to humans.” Other Proposition 65 authoritative bodies[26] use similar statements to characterize acrylamide’s carcinogenic potential. IARC uses “probably carcinogenic to humans”, NIOSH uses “potential occupational carcinogen”, and NTP uses “reasonably anticipated to be a human carcinogen” (NTP).
- clarifies that the chemical is not intentionally added by the manufacturer, but it is formed during cooking or processing at high temperatures. OEHHA chose warning language that is easy for a consumer to understand. The term “processing at high temperatures,” is found on a warning label about acrylamide exposure for baked pastries sold at a Costco retailer in California.[27]

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[24] US EPA (2010) Toxicological Review of Acrylamide, page 255. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0286tr.pdf
[25] Ibid, page 167
[26] Title 27, California Code of Regs., Subsection 25306(l)
[27] See Appendix 2, label from moon cakes sold at a Costco retailer in California and purchased in August 2021.

- notes that the frequency and amount of the chemical consumed affect a person's individual cancer risk. Including information about the factors that can affect the personal cancer risk of an individual is intended to empower the consumer to make informed choices about their individual risk prior to exposure to the listed chemical.
- points consumers to a link/location on OEHHA's warning website where they can obtain guidance on how to reduce exposures and obtain additional information about the chemical. The fact sheet on the website[28] provides additional information such as the scientific evidence on why acrylamide is considered a carcinogen, ways a person is exposed to the chemical, and tips for reducing exposure like frying foods at lower temperatures and toasting bread to the lightest color acceptable.

Each of these statements is factual, including information from the listing record for acrylamide[29] and the supporting scientific information for the regulation establishing a no significant risk level (NSRL) for acrylamide.[30]

The proposed warning includes the chemical name (acrylamide) as is required in other safe harbor warnings.[31]

IV. Necessity

OEHHA has determined that a tailored safe harbor warning for acrylamide exposures from food will provide clearer and more factual information for the benefit of the consumers who may be exposed. The proposed safe harbor language provides content that businesses can use to provide a warning if they choose to do so. It will also facilitate provision of safe harbor warnings for food in a manner that avoids the First Amendment concerns that have been raised about the more general consumer product warnings when used in the context of acrylamide exposures from foods.

V. Economic Impact Assessment Required by Gov. Code section 11346.3(b)

In compliance with Government Code section 11346.3, OEHHA has assessed all the elements pursuant to sections 11346.3(b)(1)(A) through (D).

Creation or elimination of jobs within the State of California

This regulatory action will not impact the creation or elimination of jobs within the State of California. The proposed regulation will help businesses comply with the requirements of Proposition 65 by providing nonmandatory guidance for businesses

[28] See Appendix 3, Proposition 65 Warning Website Fact Sheet
[29] See https://www.p65warnings.ca.gov/chemicals/acrylamide
[30] See https://oehha.ca.gov/media/downloads/crnr/acrylamidensrl.pdf
[31] Title 27, Cal. Code of Regs., section 25601(b)

concerning how safe harbor warnings should be provided for exposures to acrylamide from food.

Creation of new businesses or elimination of existing businesses within the State of California

This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The proposed regulation will help businesses comply with the requirements of Proposition 65 by providing non-mandatory guidance for businesses concerning how safe harbor warnings should be provided for exposures to acrylamide from food.

Expansion of businesses currently doing business within the State of California

This regulatory action will not impact the expansion of businesses within the State of California. The proposed regulation will provide non-mandatory guidance for businesses concerning how safe harbor warnings should be provided for exposures to acrylamide from food.

Benefits of the proposed regulation to the health and welfare of California residents, worker safety, and the state's environment

OEHHA has concluded that the public would benefit from the proposed amendments because they will provide a more specific warning option for businesses to use when they provide warnings for exposures to acrylamide. The action furthers the right-to-know purposes of the statute and therefore promotes public and worker health and safety.

VI. Technical, Theoretical, and/or Empirical Study, Reports, or Documents Relied Upon

Citations to documents relied on for this proposal are provided in this document. Copies of these documents will be included in the regulatory file for this action and are available from OEHHA upon request.

VII. Benefits of the Proposed Regulation

Regulated businesses that choose to follow the safe harbor provisions of the clear and reasonable warning regulations will likely benefit from the proposed amendments because they provide safe harbor protection for businesses causing exposures to acrylamide from food and provide businesses with an additional option for warning content that will be deemed "clear and reasonable." The health and welfare of California residents will likely benefit by increasing the public's ability to understand the warnings they receive for certain food they purchase. The public will also benefit from the link to the Proposition 65 warnings website where OEHHA provides scientific information about the carcinogenicity of acrylamide, how exposure occurs, how to reduce exposure,

and information on acrylamide in an easy-to-read facts sheet and readily accessible links to additional information.

VIII. Reasonable Alternatives to the Regulation and the Agency's Reasons for Rejecting Those Alternatives

OEHHA has determined there are no reasonable alternatives to the proposed regulatory action that would carry out the purposes of the Act. The proposed action provides an optional safe harbor warning that a business can choose to use or not.

IX. Reasonable Alternatives to the Proposed Regulatory Action that Would Lessen Any Adverse Impact on Small Business and the Agency's Reasons for Rejecting Those Alternatives

OEHHA has initially determined that no reasonable alternative considered by OEHHA, or that has otherwise been identified and brought to its attention, would be more effective in carrying out the proposed action, or would be as effective and less burdensome to small business, or would be more cost-effective and equally effective in implementing the statutory policy or other provision of law to small business. The current proposal furthers the purposes of Proposition 65 by providing non-mandatory guidance for businesses concerning how safe harbor warnings can be provided for exposures to acrylamide from food.

X. Evidence Supporting Finding of No Significant Adverse Economic Impact on Business

OEHHA does not anticipate that the regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. The proposed regulatory action will provide non-mandatory guidance for businesses, including content for a warning for exposures to acrylamide from food.

XI. Efforts to Avoid Unnecessary Duplication or Conflicts with Federal Regulations Contained in the Code of Federal Regulations Addressing the Same Issues

Proposition 65 is a California law that has no federal counterpart. OEHHA has determined that the regulations do not duplicate and will not conflict with federal regulations.

XII. Appendices

Appendix 1: Scientific evidence on acrylamide carcinogenicity

Evidence on acrylamide carcinogenicity from animal studies

Acrylamide is a multisite carcinogen in animals, causing statistically significant increases in the incidence of tumors in male and female rats[32,33,34] and male and female mice[35,36,37,38].

In the studies conducted prior to NTP's two-year cancer bioassays (2012)[39], acrylamide caused statistically significant increases in the incidence of tumors in male and female rats[40,41] and male and female mice[42,43,44]. In male rats, acrylamide induced tumors of the thyroid gland, testis, and central nervous system. In female rats, acrylamide induced tumors in the thyroid gland, oral cavity, mammary gland, uterus, clitoral gland, and the central nervous system. In studies of male mice examining only the lung, acrylamide produced lung tumors. In studies of female mice examining only the lung and skin, acrylamide produced lung and skin tumors.

In 2012, NTP published the technical report for two-year cancer bioassays conducted in F344/N rats and B6C3F1 mice[45]. Under the conditions of these two-year drinking water studies, NTP (2012) concluded that:

- There was clear evidence of carcinogenic activity of acrylamide in male F344/N rats based on increased incidences of malignant mesothelioma of the epididymis and testis tunica, malignant schwannoma of the heart, and follicular cell

[32] Johnson KA, Gorzinski SJ, Bodner KM, Campbell RA, Wolf CH, Friedman MA et al. (1986). Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol Appl Pharmacol 85(2):154-168.
[33] Friedman MA, Dulak LH, Stedham MA (1995). A lifetime oncogenicity study in rats with acrylamide. Fundam Appl Toxicol 27(1):95-105.
[34] National Toxicology Program (NTP, 2012). Toxicology and Carcinogenesis Studies of Acrylamide in F344/N Rats and B6C3F1 Mice (Feed and Drinking Water Studies). TR No. 575. US Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr575_508.pdf
[35] Bull RJ, Robinson M, Stober JA (1984b). Carcinogenic activity of acrylamide in the skin and lung of Swiss-ICR mice. Cancer Lett 24(2):209-212.
[36] Bull RJ, Robinson M, Laurie RD, Stoner GD, Greisiger E, Meier JR, Stober, J (1984a). Carcinogenic effects of acrylamide in Sencar and A/J mice. Cancer Res 44(1):107-111.
[37] Robinson M, Bull RJ, Knutsen GL, Shields RP, Stober J (1986). A combined carcinogen bioassay utilizing both the lung adenoma and skin papilloma protocols. Environ Health Perspect 68:141-145.
[38] NTP (2012), full citation provided in footnote 34.
[39] *Ibid*.
[40] Johnson et al. (1986), full citation provided in footnote 32.
[41] Friedman et al. (1995), full citation provided in footnote 33.
[42] Bull et al. (1984b), full citation provided in footnote 35.
[43] Bull et al. (1984a), full citation provided in footnote 36.
[44] Robinson et al. (1986), full citation provided in footnote 37.
[45] NTP (2012), full citation provided in footnote 34.

adenoma or carcinoma of the thyroid gland. An increased incidence of pancreatic islet adenoma was also considered related to acrylamide exposure.

- There was clear evidence of carcinogenic activity of acrylamide in female F344/N rats based on increased incidences of fibroadenoma of the mammary gland, squamous cell neoplasms (primarily papilloma) of the oral cavity (mucosa or tongue), mesenchymal neoplasms (fibroma, fibrosarcoma, or sarcoma) of the skin, and follicular cell neoplasms (adenoma or carcinoma) of the thyroid gland. Increased incidences of hepatocellular adenoma of the liver and carcinoma of the clitoral gland were also considered to be related to acrylamide exposure. The occurrence of malignant schwannoma of the heart may have been related to acrylamide exposure.
- There was clear evidence of carcinogenic activity of acrylamide in male B6C3F1 mice based on increased incidences of neoplasms (primarily adenoma) of the harderian gland, alveolar/bronchiolar neoplasms (primarily adenoma) of the lung and squamous cell neoplasms (primarily papilloma) of the forestomach.
- There was clear evidence of carcinogenic activity of acrylamide in female B6C3F1 mice based on increased incidences of harderian gland adenoma, alveolar/ bronchiolar adenoma of the lung, adenoacanthoma and adenocarcinoma of the mammary gland, benign granulosa cell neoplasms of the ovary, and malignant mesenchymal neoplasms of the skin. Increased incidences of squamous cell papilloma of the forestomach were also considered to be related to acrylamide exposure.

Glycidamide is the genotoxic metabolite for acrylamide in humans as well as in animals. In 2014, NTP published the technical report for two-year cancer bioassays on glycidamide in rats and mice[46]. Similar to the findings from NTP (2012) on acrylamide, NTP's two-year cancer bioassays on glycidamide also concluded that there was clear evidence of carcinogenicity in multiple tumor sites in male and female rats and mice.

Applicability of animal and other experimental studies of acrylamide to humans

These animal studies provide strong support for a finding that acrylamide causes cancer in humans. It is a fundamental tenet of toxicology that the results of properly designed studies in experimental animals are applicable to humans. See also 29 C.F.R. § 1910.1220, app. A.6.1. (Federal Occupational Safety and Health Administration regulations): this principle applies "unless there is strong evidence that the mechanism for tumor formation is not relevant to humans". In the case of acrylamide, the genotoxic mechanism of action through its metabolite glycidamide, has been proven to be applicable in humans.

[46] National Toxicology Program (NTP 2014). Toxicology and Carcinogenesis Studies of Glycidamide in F344/N Nctr Rats and B6C3F1/Nctr Mice (Drinking Water Studies). TR No. 588. US Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. Available from: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr588_508.pdf

In a chapter within the widely respected reference *Patty's Toxicology*, Rachamin (2015)[47] discussed the value of animal studies in predicting human health risks:

> "Studies of experimental animals provide the main source of data for assessing chemical safety. They provide information on the toxicity of a chemical under controlled experimental conditions (dose levels, effects measured, population size). Animal toxicity tests are particularly important because they provide an opportunity to identify toxic chemicals before people are actually exposed to them and, therefore, prevent potential adverse health effects.
>
> In general, animal studies have a high predictive value for human health risks. Almost all known chemical carcinogens in humans cause cancer in some animal species. Further, it has been shown that exposure of animals to toxic agents in high doses is a valid method for discovering potential hazards to humans."

The predictive value of animal studies is supported by the fact that mouse and human genomes are highly similar and share about 97.5% of their protein-coding DNA[48]. In rats, almost all human genes that are associated with human diseases have orthologues in the rat genome, confirming that rats also are an excellent model for research on human health[49].

The IARC (2019) Preamble to the IARC Monographs on the Identification of Carcinogenic Hazards to Humans[50] states the following regarding the relevance of data from carcinogenicity studies in animals in assessing human cancer hazards:

> "Although this observation cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is sufficient evidence of carcinogenicity in experimental animals (see Part B, Section 6b) present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, such as strong evidence that a given agent causes cancer in experimental animals through a 6 species-specific mechanism that does not operate in humans (see Part B, Sections 4 and 6; Capen et al., 1999; IARC, 2003), these agents are considered to pose a potential carcinogenic hazard to humans."

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[47] Rachamin G (2015). Use of Toxicological Data in Evaluating Chemical Safety. In Patty's Toxicology (eds E. Bingham, B. Cohrssen and C.H. Powell). Available from: https://onlinelibrary.wiley.com/doi/10.1002/0471435139.tox010

[48] Mural RJ, Adams MD, Myers EW, Smith HO, Miklos GL, Wides R, et al. (2002). A comparison of whole-genome shotgun-derived mouse chromosome 16 and the human genome. Science 296 (5573):1661-71.

[49] Rat Genome Sequencing Project Consortium (2004). Genome sequence of the Brown Norway rat yields insights into mammalian evolution. Nature 428**,** 493–521. Available from: https://doi.org/10.1038/nature02426

[50] IARC (2019). Preamble to the IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Lyon, France. Amended January 2019. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf

In its Handbook for Preparing Report on Carcinogens Monographs[51], NTP makes a similar statement:

> "Neoplasms observed in experimental animals are considered to be relevant to humans unless there is compelling evidence indicating that they occur by a mechanism that does not operate in humans."

US EPA routinely relies on long-term carcinogenicity in rodents in its risk assessment activities, and stated the following regarding applicability of animal studies and importance of mechanistic information in its 2005 Guidelines for Carcinogen Risk Assessment[52]:

> "In these cancer guidelines, tumors observed in animals are generally assumed to indicate that an agent may produce tumors in humans. Mode of action may help inform this assumption on a chemical-specific basis."
>
> "In the absence of sufficiently, scientifically justifiable mode of action information, EPA generally takes public health-protective, default positions regarding the interpretation of toxicologic and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity."

In summary, both animal toxicology studies and cell-based studies are essential to discerning whether chemicals cause cancer. In the case of acrylamide, the evidence is clear from both the animal cancer bioassays and mechanistic studies including studies using human cells. The genotoxicity of both acrylamide and its reactive metabolite glycidamide are well-studied. Acrylamide is a mutagen in *in vitro* studies and induces mutations in animal studies. It can also cause chromosomal and DNA damage in animal studies and mammalian *in vitro* studies[53]. Although acrylamide appears to be a relatively weak mutagen in short-term mutagenicity assays, in humans, it causes mutations primarily through its metabolism to glycidamide, which is a much stronger mutagen. In addition, acrylamide can induce gene mutations by generating reactive oxygen species and oxidative DNA damage[54].

Besides the evidence in animals, genetic analysis of human cancers by scientists from IARC, National Center for Toxicological Research (NCTR), and other leading cancer

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[51] NTP (2015). National Toxicology Program Handbook for Preparing Report on Carcinogens Monographs. US Department of Health and Human Services. Available from: https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/handbook/index.html

[52] US Environmental Protection Agency (US EPA 2005). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F. Available from: https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

[53] NTP (2012), full citation provided in footnote 34.

[54] European Food Safety Authority (EFSA 2015). EFSA Panel on Contaminants in the Food Chain (CONTAM). Scientific Opinion on acrylamide in food. *EFSA Journal* 13(6):4104. Available from: https://www.efsa.europa.eu/en/efsajournal/pub/4104

research institutions has revealed a potentially large contribution from acrylamide. Specifically, the unique mutational signature of glycidamide was found in one third of 1600 human tumor genomes, corresponding to 19 human tumor types from 14 organs. As mentioned above, glycidamide is the major reactive metabolite of acrylamide[55] and its major source of exposure in humans is through exposure to acrylamide. As pointed out by NTP (2014)[56], "[t]he major source of human exposure to glycidamide occurs through exposure to acrylamide either in occupational situations, through the diet, or by the use of tobacco products". This study provides robust mechanistic evidence for the mutagenic effects of acrylamide exposure in humans[57].

Inadequacy of human epidemiological studies for determining acrylamide carcinogenicity

Thus far, epidemiological studies have yielded inconsistent and inconclusive data on the association between acrylamide exposure and cancers in humans. A major challenge in conducting dietary epidemiological studies is the difficulty in estimating dietary intake of acrylamide.

An essential element of epidemiological studies is the correct classification of the study subjects' exposure. This is especially difficult in studies of dietary exposure to acrylamide. This difficulty is evident in those studies that utilize self-reported dietary assessments such as food frequency questionnaires or 24-hour dietary recalls. Self-reported dietary assessments are useful for assessing dietary patterns, but they were not designed for capturing chemical exposures[58]. The content of acrylamide in foods is quite variable and depends on a number of factors, including ingredients, cooking method, length of cooking, temperature at which foods were processed, storage of food, micronutrient composition of the raw food, and other factors. Self-reported dietary assessments are not able to consider all these features, and therefore are not able to correctly categorize an individual's exposure to acrylamide. Additionally, acrylamide is present in a wide range of foods, and self-reported dietary assessments likely underestimate actual acrylamide intake. Abt et al. (2019) note:

> "The occurrence of acrylamide in a wide range of foods, and at variable levels, together with the variation in intake of foods containing acrylamide, present a challenge for accurately determining acrylamide exposure and complicate efforts

[55] Zhivagui M, Ng AWT, Ardin M, Churchwell MI, Pandey M, Renard C, et al. (2019). Experimental and pan-cancer genome analyses reveal widespread contribution of acrylamide exposure to carcinogenesis in humans. Genome Res 29(4):521-531. Available from: https://genome.cshlp.org/content/29/4/521
[56] NTP (2014), full citation provided in footnote 46.
[57] IARC (2019). Press Release Nº 267. Experimental and pan-cancer genome analyses reveal widespread contribution of acrylamide exposure to carcinogenesis in humans. Lyon, France. March 7, 2019. Available from: https://www.iarc.who.int/wp-content/uploads/2019/03/pr267_E.pdf
[58] Virk-Baker MK, Nagy TR, Barnes S, Groopman J. (2014). Dietary acrylamide and human cancer: a systematic review of literature. Nutr Cancer 66(5):774-90.

to establish an association between acrylamide exposure from food and cancer risk."[59]

To understand if self-reported dietary assessments correctly estimate acrylamide exposure, Ferrari et al. (2013)[60] compared self-reported dietary assessments to acrylamide-hemoglobin adducts measured in blood, which is a biomarker of acrylamide exposure. The study found that estimates of acrylamide intake based on self-reported diet did not correlate well with biomarker levels, showing that self-reported dietary assessments are not able to accurately measure acrylamide exposure.

The consequence of this type of exposure misclassification is that it is difficult to detect an association, i.e., statistical power is reduced. Imprecise exposure measurement reduces the apparent relative risk and may generate misleading conclusions.

Acrylamide is ubiquitous in the diet. It is estimated that more than one-third of the calories consumed in the US comes from food that contains acrylamide. This makes study of dietary acrylamide exposures and cancer especially challenging with respect to the exposure misclassification issue. As noted by one prominent research group[61],

> "In the reviewed epidemiologic studies, the dietary acrylamide exposure assessment has been inadequate leading to potential misclassification. In addition, the case-control studies have reported nearly same magnitude of dietary acrylamide exposures among both cases and controls. For disease end-point such as cancer, the exposure assessment methods that could capture the long-term exposures are highly recommended. However, majority of the reviewed epidemiologic studies have rather estimated one-time point exposures from the baseline FFQs [food frequency questionnaires] with the huge assumption that the dietary acrylamide content as well as the individual exposures over time remained constant. This is especially worrisome since a number of new food items are introduced in the market each year. In addition, food consumption patterns can be influenced by factors such as seasonality, prices, sales, as well as social factors such as holidays etc. resulting in potential changes in dietary acrylamide exposure."
>
> "…Until we have the improved exposure assessment methods incorporated, the epidemiologic studies assessing relationship between dietary acrylamide and cancer will not have any meaningful interpretations."

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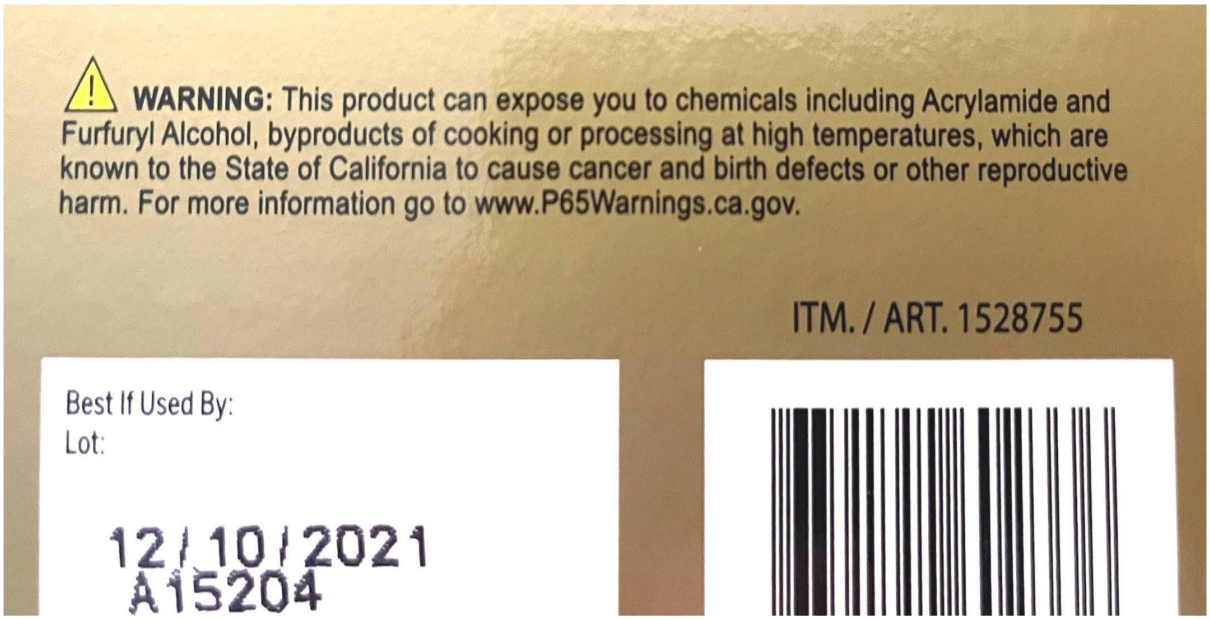
[59] Abt E, Robin LP, McGrath S, Srinivasan J, DiNovi M, Adachi Y, Chirtel S. (2019). Acrylamide levels and dietary exposure from foods in the United States, an update based on 2011-2015 data. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 36(10):1475-1490.
[60] Ferrari P, Freisling H, Duell EJ, Kaaks R, Lujan-Barroso L, Clavel-Chapelon F, et al. (2013). Challenges in estimating the validity of dietary acrylamide measurements. Eur J Nutr 52(5):1503-12.
[61] Virk-Baker MK, Nagy TR, Barnes S, Groopman J. Dietary acrylamide and human cancer: a systematic review of literature. *Nutr Cancer*. 2014;66(5):774-790. doi:10.1080/01635581.2014.916323

Thus, it is crucial to integrate evidence from other data sources, i.e., animal, and mechanistic studies[62].

[62] NTP (2015), full citation provided in footnote 51.

Appendix 2: Warning label from moon cakes sold at a Costco retailer in California



Appendix 3: Proposition 65 Warning Website Fact Sheet

OEHHA
SCIENCE FOR A HEALTHY CALIFORNIA

Proposition 65 Warnings
Office of Environmental Health Hazard Assessment
www.P65Warnings.ca.gov

PROPOSITION 65
Your right to know!

Acrylamide

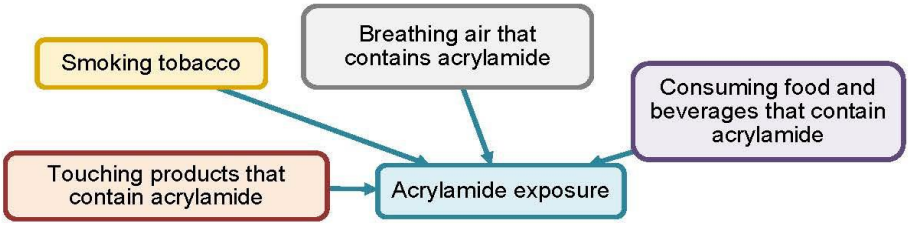
Why am I being warned about potential exposure to acrylamide?

- Acrylamide is on the Proposition 65 list because it can cause cancer. Exposure to acrylamide may increase the risk of cancer.
- Acrylamide is also on the Proposition 65 list because it can cause birth defects or other reproductive harm. It can affect the development of the fetus and can harm the male reproductive system. Levels in food are generally well below the levels currently believed to cause these harmful effects.
- Proposition 65 requires businesses to determine if they must provide a warning about significant exposure to listed chemicals.

What is acrylamide?

- Acrylamide is a chemical that is formed in certain plant-based foods during cooking or processing at high temperatures, such as frying, roasting, grilling, and baking. Boiling or steaming foods does not create acrylamide.
  - Sources of acrylamide in the diet include french fries, potato chips, other fried and baked snack foods, roasted asparagus, canned sweet potatoes and pumpkin, canned black olives, roasted nuts, roasted grain-based coffee substitutes, prune juice, breakfast cereals, crackers, some cookies, bread crusts, and toast.
  - Researchers discovered the presence of acrylamide in fried, roasted, and other cooked foods in 2002. High temperatures during cooking convert sugars and other naturally occurring substances in these foods to acrylamide.
- Tobacco smoke contains acrylamide.
- Acrylamide is used for industrial purposes. It has been used in grouts and cements. It is also used to produce polyacrylamide.

How does exposure to acrylamide occur?



- During pregnancy, acrylamide can pass from mother to baby.

How can I reduce my exposure to acrylamide?

® Do not smoke. Do not allow children to breathe tobacco smoke.

The US Department of Health and Human Services recommends:

- Adopt a healthy, balanced eating plan that includes fruits, vegetables, lean meats, fish, high-fiber grains, and beans.
- Fry foods at 170 degrees Celsius (338 degrees Fahrenheit) or lower temperatures. *[The higher the frying temperature, the more acrylamide* is *formed].*
  - *[If you do not have a "deep fry" thermometer, dip a wooden chopstick or wooden spoon handle into the oil. If the oil slowly* starts *to bubble and the bubbles are* small, *then the oil* is *hot enough for frying. If the oil bubbles rapidly, with large bubbles, then the oil* is *too hot.]*
- Cook potato strips, such as french fries, to a golden yellow rather than a golden brown color. *[Longer cooking times result in greater formation of acrylamide.]*
- Toast bread to the lightest color acceptable.
- Soak raw potato slices in water for 15-30 minutes before frying or roasting. Drain and blot dry before cooking. *[Soaking in water removes* some *of the precursors to acrylamide formation.]*

® Do not store raw potatoes in the refrigerator. *[Cold temperatures increase the sugar content of potatoes. Sugars are precursors to acrylamide formation.]*

For more information:

General Fact Sheets and Resources

- American Cancer Society
  - Acrylamide and Cancer Risk
    https://www.cancer.org/cancer/cancer-causes/acrylamide.html

Acrylamide in Food

- US Department of Health and Human Services (HHS)
  National Institutes of Health (NIH)
  - Acrylamide
    https://www.niehs.nih.gov/health/topics/agents/acrylamide/index.cfm
  - Acrylamide and Cancer Risk
    https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/acrylamide-fact-sheet

  US Food and Drug Administration (FDA)
  - Acrylamide
    https://www.fda.gov/food/chemicals/acrylamide

Scientific Information on Acrylamide

- California Environmental Protection Agency (CalEPA)
  Office of Environmental Health Hazard Assessment (OEHHA)
  - ▶ Characterization of Acrylamide Intake from Certain Foods
    http://oehha.ca.gov/media/downloads/crnr/acrylamideintakereport.pdf
- National Toxicology Program (NTP)
  - ▶ NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide
    https://ntp.niehs.nih.gov/ntp/ohat/acrylamide/acrylamide_monograph.pdf

Proposition 65

- California Environmental Protection Agency (CalEPA)
  Office of Environmental Health Hazard Assessment (OEHHA)
  - ▶ Proposition 65: Background
    https://www.p65warnings.ca.gov/faq
  - ▶ Proposition 65: The List of Chemicals
    https://www.p65warnings.ca.gov/chemicals
  - ▶ Proposition 65: Fact Sheets
    https://www.p65warnings.ca.gov/fact-sheets