FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

ADOPTION OF NEW SECTION 25704
EXPOSURES TO LISTED CHEMICALS IN COFFEE
POSING NO SIGNIFICANT RISK

California Environmental Protection Agency

Office of Environmental Health Hazard Assessment

CONTENTS

GENERAL INFORMATION

This is the Final Statement of Reasons for the adoption of a new section 25704 in Title 27 of the California Code of Regulations[1]. The new section 25704 states that exposures to Proposition 65-listed chemicals in coffee that are produced as part of and inherent in the processes of roasting coffee beans and brewing coffee pose no significant risk of cancer.

Process and Timeline

On June 22, 2018, the Office of Environmental Health Hazard Assessment (OEHHA) published a Notice of Proposed Rulemaking to adopt the new section 25704. The scientific basis for the proposed regulation was discussed in the Initial Statement of Reasons (ISOR)[2].

On August 16, 2018, OEHHA received oral comments on the proposed rulemaking at a public hearing. OEHHA received written public comments for the proposed rulemaking during the initial comment period, which ran from June 22 to August 30, 2018. In addition, pursuant to section 25701(e) and Health and Safety Code section 57004, OEHHA provided the Notice of Proposed Rulemaking, the proposed regulatory text and the ISOR to members of the Carcinogen Identification Committee for peer review. OEHHA's responses to the public and peer review comments received during this rulemaking are incorporated within this Final Statement of Reasons (FSOR).

On March 15, 2019, OEHHA announced a 15-day public comment period on amendments to the proposed regulation that would add clarity concerning which listed chemicals are covered by the regulation. The amendments clarify that the regulation applies to any chemicals in coffee listed on or before March 15, 2019 as known to the state to cause cancer that are created by and inherent in the processes of roasting coffee beans or brewing coffee.

OEHHA's Conclusions

OEHHA has carefully read and considered all the comments received on this proposed rulemaking. Taking into account all the relevant comments, OEHHA's overall conclusion has not changed. The available scientific information, including the 2018 Monograph on Drinking Coffee by the International Agency for Research on Cancer

[1] All further references are to sections of Title 27, Cal. Code of Regs., unless indicated otherwise.
[2] OEHHA (2018), Initial Statement of Reasons, Title 27, California Code of Regulations, Adoption of a New Section 25704, Exposures to Listed Chemicals in Coffee Posing No Significant Risk, OEHHA, California Environmental Protection Agency.

(IARC)[3], an authoritative body for purposes of Proposition 65[4], supports OEHHA's determination that exposures to listed chemicals in coffee created by roasting coffee beans or brewing coffee do not pose a significant risk of cancer for purposes of Proposition 65. The weight of the evidence from the very large number of studies in the scientific literature does not support an association between the complex mixture of chemicals that is coffee[5] and a significant risk of cancer. OEHHA's key overall considerations in adopting this regulation are as follows:

- There is inadequate evidence for the carcinogenicity of drinking coffee, based on a very large number of human studies[6].
- There are inverse associations – decreasing risk with increasing coffee consumption - for human cancers of the liver and uterine endometrium[7].
- There is inadequate evidence of increased carcinogenicity in animals administered coffee in controlled experiments.
- There are inverse associations in a number of animal experiments and the overall evidence from animal studies is that of reduced incidence or reduced multiplicity of cancers with coffee intake.
- There is a rich mix of cancer-preventative agents in brewed coffee.

Taken together, these considerations form the basis for OEHHA's determination that exposure to listed chemicals in coffee, that are created by and inherent in the processes of roasting or brewing coffee, does not pose a significant cancer risk under Proposition 65. Therefore, providing warnings for such exposures would not be "clear and reasonable" or consistent with the purpose of Proposition 65[8].

[3] International Agency for Research on Cancer (IARC 2018). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Drinking Coffee, Mate, and Very Hot Beverages, Volume 116, World Health Organization, Lyon, France. Available at https://publications.iarc.fr/566.
[4] See Section 25306(m) of the implementing regulations.
[5] See ISOR, page 4 (internal citations omitted): "Coffee," as referenced in this document and the proposed regulation, refers to a beverage made by percolation, infusion, or decoction from the roasted seeds of a coffee plant. Coffee is a unique and complex chemical mixture that contains numerous chemicals formed during the roasting of coffee beans. Chemicals are also formed during the brewing of coffee.
[6] Explained on p.12 of the ISOR as "a lack of evidence showing increases in cancers". See also p. 11 of the ISOR: "[coffee] has not been found to increase the risk of any cancers" (citing p. 425 of 2018 IARC Monograph).
[7] Explained on p. 12 of the ISOR as "reductions of specific cancers resulting from coffee drinking". See also p. 11 of the ISOR: "[coffee] is associated with reduced risk of some cancers" (citing p. 425 of 2018 IARC Monograph).
[8] See discussion of the definition of "coffee" and discussion of the scope of chemicals covered and not covered by the proposed regulation in the ISOR at pages 3, 4 and 12.

OEHHA's summary of the relevant comments received and its responses are set out below.

COMMENTERS

Public Commenters

OEHHA received oral comments on the proposed regulatory action from nine individuals during the August 16, 2018 public hearing. The individuals providing comments along with their affiliations are provided in Table 1 below. Also shown in the left column of the table is a designation by which the individual commenter will be referenced in the responses to comments.

Written public comments were received from a number of individuals. Individuals submitting comments along with their affiliations are shown in Table 2. Also shown in Table 2 are the designations by which the submission will be referenced in the summary of and responses to comments.

Several written and oral comments submitted during the regulatory process included observations about these regulations or other laws and regulations that do not constitute an objection or recommendation directed at the proposed action or the procedures followed in this rulemaking action. In addition, many parties offered their interpretation of these regulations or other laws and regulations, sometimes in connection with their support of, or decision not to object to the regulation, which does not constitute an objection or recommendation directed at changing the proposed action or the procedures followed in this rulemaking process. OEHHA is not required under the Administrative Procedure Act (APA) to respond to such remarks in the rulemaking and therefore is not providing responses to all of these comments in this FSOR. However, the absence of responses to such comments should not be construed to mean that OEHHA in any way agrees with them.

Table 1. Oral public comments made at the August 16, 2018 public hearing

Designation	Commenter
CERT H1	Raphael Metzger, Council for Education and Research on Toxics (CERT)
NCA H2	William Murray, National Coffee Association (NCA)
NCA H3	Dr. Alan Leviton, Harvard University, on behalf of National Coffee Association
NCA H4	Trent Norris, Arnold and Porter, on behalf of National Coffee Association
CRA H5	Jeffrey Margulies, Norton, Rose Fulbright, on behalf of California Retailers Association (CRA)

Designation	Commenter
Canteen H6	Robert Donohue, Canteen Vending
Hornung H7	John Hornung
CalChamber H8	Adam Regele, on behalf of California Chamber of Commerce (CalChamber)
NAMA/CAVC H9	Sandra Larson, on behalf of Northwest Automatic Vending Association (NAMA) and California Automatic Vendors Council (CAVC)

Table 2. Written public comments received during the initial comment period

Designation	Organization Commenters
CAVC	California's Automatic Vendors Council, submitted by Sandra Larson
CSPI	Center for Science in the Public Interest, submitted by Peter Lurie and Lisa Lefferts
CTWG	Chemical Toxin Working Group, submitted by David Steinman
CERT 1-19	Council for Education and Research on Toxics (CERT), 19 separate submissions by Raphael Metzger (see Table 3)
FDA	US Food and Drug Administration, submitted by Susan Mayne, Director, Center for Food Safety and Applied Nutrition
HIKCC	Hawaiian Isles Kona Coffee Company, submitted by James Twietmeyer
Industry Coalition	Industry coalition letter[9], submitted by John Hewitt, Grocery Manufacturers Association
Mountanos	M. P. Mountanos, submitted by Richard Kourafas
NCA	National Coffee Association, USA, submitted by William Murray, Mark Corey, and Alan Leviton[10]
NConfA	National Confectioners Association, submitted by Laura Shumow
Philz	Philz Coffee, submitted by Andi Trindle Mersch
SCA	Specialty Coffee Association, submitted by Peter Guiliano
Designation	**Individuals Commenting**
Anonymous 1	Anonymous, "Concerned Coffee Drinker"
Anonymous 2	Anonymous (submitted 8/8/18, 10:38 am)
Bayard	Steven Bayard
Bob L.	Bob L.

[9] Signed by Emily Rooney (Agricultural Council of California), Michael Shaw (California Manufacturers & Technology Association), Fredericka McGee (American Beverage Association), Matthew Sutton (California Restaurant Association), Tim Shestek (American Chemistry Council), Pamela Williams (California Retailers Association), Adam Regele (California Chamber of Commerce), John Doherty (Civil Justice Association of California), Aaron Moreno (California Grocers Association), John Hewitt (Grocery Manufacturers Association), and Trudi Hughes (California League of Food Producers)

[10] NCA cited a number of publications in its comments.

Designation	Organization Commenters
CSI	Convenience services industry: Identical submissions from 25 individuals.[11]
Clark	Gare Clark
Cody	Cody
Coughlin	James R. Coughlin, Coughlin and Associates
Eaton 1	Josh Eaton
Eaton 2	Jim Eaton
Glasser	Greg Glasser
Hornung	John Hornung
Hotchkis	Remington Hotchkis
Infante	Peter F. Infante, Peter F. Infante Consulting, LLC
Kamangar	Farin Kamangar, Morgan State University, Baltimore MD
Lilla	William M. Lilla
Melnick	Ronald L. Melnick
Miller	Carl Miller
Smith	Martyn Smith, University of California, Berkeley, School of Public Health. Submitted as an individual opinion
Sriboonwong	Irene Sriboonwong
Tim J.	Tim J.
Trinity	TrinityCBC

CERT provided written comments in 19 different submissions; these are listed in Table 3 below. They include one submission of comments on the Initial Statement of Reasons (CERT 18) and one legal brief in opposition to the proposed regulation (CERT 19). The 17 other submissions (CERT 1-17) in large part are opinions and transcripts of expert testimony in legal proceedings from 2007-2017, a number of which are referred to in CERT's comments on the ISOR (CERT 18). These 17 documents are not directly relevant to the proposed regulation, having been prepared or submitted during a civil trial of a private enforcement matter. OEHHA does not concede that any of the material in the 17 submissions requires a response.

Four experts who testified or submitted statements in the private enforcement case contained in CERT 1-17 also separately submitted comments as individuals during the public comment period on the proposed regulation: Drs. Bayard, Smith, Infante, and Melnick. These separate individual submissions are referred to using the designations in Table 2 above.

[11] Robert Donohue, Jason Eberstein, Amanda Sulc, Linda Furlano, David Postian, Devin Smith, Stuart Harris, Andrew Cleveland, Kelley Dayton, Larry Atnip, Matthew Marsh, Ken Burton, Amy Fox-Bartley, Charles Griggs, Mark Cone, Brad Olney, Alishia Zaldivar, Thomas DePaola, Paul Tullio, Lawrence Shoemaker, Jack Brown, CJ Recher, Scott Boyd, Mickal McMath, and Jeffrey Duerr

Table 3. Raphael Metzger Submissions on behalf of CERT during the initial comment period

Designation	Submission Contents
CERT 18	CERT – Specific comments on the Initial Statement of Reasons CERT also submitted a flash drive containing 902 references cited in its comments on the statement of reasons Ex A: Loomis et al. Lancet Oncol 17: 877, 2016 Ex B: IARC July 2016 Q&A on Monograph 116 Ex C: FDA 2009 Guidance for Industry: Evidence-Based Review System for Scientific Evaluation of Health Claims Ex D: Jiang et al. Gynecol Oncol, 129:620, 2013 Ex E: Sept 2015 CERT v Starbucks Statement of Decision on Trial (Phase 1) Ex F: May 2018 CERT v Starbucks Statement of Decision on Trial (Phase 2) Ex G: CERT v Starbucks order declassifying and unsealing documents regarding the relationship between GMA and its members
CERT 19	CERT legal brief in opposition to the proposed regulation
CERT 1	Exhibit (Ex) A: September 2017 testimony of D Alexander in CERT v Starbucks Ex B: D Alexander Curriculum Vitae
CERT 2	Ex A: April 22, 2014 Statement of SP Bayard Ex B: May 24, 2014 corrected SP Bayard statement Ex C: April 28, 2014 errata
CERT 3	Ex A: Statement of SP Bayard; Ex B: October 2014 testimony of SP Bayard in CERT v Starbucks Ex C: SP Bayard resume
CERT 4	Ex A: Summary of Opinions of N Brautbar Ex B: June 2016 Curriculum Vitae of N Brautbar
CERT 5	Ex A: Opinions of JE Huff Ex B Acrylamide, glycidamide, methyloacrylamide tumor site comparisons; Ex C-D: October 22, 2014 JE Huff testimony in CERT v Starbucks Ex E: JE Huff biography Ex F: JE Huff publications
CERT 6	Ex A: 2014 Opinions of PF Infante regarding cancer epidemiology of coffee Ex B: 2017 Opinions of PF Infante Ex C-E: October 2014 Testimony of PF Infante in CERT v Starbucks Ex F-G: September 2017 Testimony of PF Infante in CERT v Starbucks
CERT 7	Ex A: 2014 PF Infante opinions regarding the epidemiology of acrylamide Ex B: 2014 PF Infante conclusions regarding acrylamide cancer epidemiology Ex C-E: October 2014 Testimony of PF Infante in CERT v Starbucks Ex F: Curriculum vitae of PF Infante
CERT 8	Ex A: Opinions of J James Ex B: Curriculum Vitae of J James
CERT 9	Ex A: Opinions of LM Juliano Ex B: Sept 2017 testimony of LM Juliano in CERT v Starbucks Ex C: Curriculum vitae of Laura Juliano

Table 3 continued. Raphael Metzger Submissions on behalf of CERT during the initial comment period

Designation	Submission Contents
CERT 10	Ex A: May 2016 Declaration of RL Melnick in support of plaintiffs motion for summary adjudication of defendant's alternative significant risk level Ex B: 2017 Melnick critique of W Ristenpart's report and testimony Ex C-E: October 2017 Testimony of RL Melnick in CERT v Starbuck's Ex F: Curriculum vitae of RL Melnick
CERT 11	Ex A: 2014 conclusions of RL Melnick regarding risk assessment of exposure to acrylamide from consumption of coffee Ex B: RL Melnick critique of L Rhomberg report and testimony Ex C-E: October 2014 RL Melnick testimony in CERT v Starbucks Ex F-H: October 2017 RL Melnick testimony in CERT v Starbucks Ex I: Curriculum vitae of RL Melnick
CERT 12	Ex A: 2017 Opinions of RL Melnick Ex B: 2017 "Assessing the benefits and risks of acrylamide in coffee" Ex C: 2017 Critique of D Kessler's report and testimony Ex D-F: October 2017 RL Melnick testimony in CERT v Starbucks Ex G: Curriculum vitae of RL Melnick
CERT 13	Ex A: April 2014 SM Rappaport critique of Petersen exposure assessment of acrylamide in coffee Ex B-C: October 2014 SM Rappaport testimony in CERT v Starbucks Ex D: Curriculum vitae of SM Rappaport
CERT 14	Ex A: August 2007 opinions of SM Rappaport in CERT v McDonald's Ex B: April 2014 opinions of SM Rappaport in CERT v Starbucks Ex C: Linearity of acrylamide tumor incidence Ex D: Critique of M Dourson report Ex E: October 2014 testimony of SM Rappaport in CERT v Starbucks
CERT 15	Ex A: August 2007 opinions of SM Rappaport in CERT v McDonald's Ex B: April 2014 opinions of SM Rappaport in CERT v Starbucks Ex C: SM Rappaport's critique of J Swenberg's acrylamide mutation threshold hypothesis Ex D: October 2014 testimony of SM Rappaport in CERT v Starbucks Ex D: Curriculum vitae of SM Rappaport
CERT 16	Ex A: 2007 opinions of MT Smith in CERT v McDonald's Ex B: 2014 opinions of MT Smith in CERT v Starbucks Ex C: October 2014 Testimony of MT Smith in CERT v Starbucks Ex D: Curriculum vitae of MT Smith
CERT 17	Ex A: 2017 Opinions of JD Stookey Ex B: Biosketch of JD Stookey

During the comment period on the amendments to the proposed regulatory text, open from March 15, 2019 to April 2, 2019, OEHHA received one comment from the NCA

and a submission from CERT requesting an extension to the comment period and explanation for the modifications. OEHHA denied the request but informed CERT that it would consider its comments if submitted by the close of business on April 8, 2019.

Peer Reviewers

Pursuant to Health and Safety Code section 57004, and Title 27 Cal. Code of Regulations, sections 25302(a) and 25701(e), OEHHA in June 2018 provided the Notice of Proposed Rulemaking, the proposed regulatory text and the ISOR for the proposed regulation to members of the Carcinogen Identification Committee for individual peer review. OEHHA received peer review comments from the following committee members:

- Dr. Jason Bush
- Dr. Shanaz Dairkee
- Dr. Joseph Landolph
- Dr. Thomas Mack
- Dr. Thomas McDonald

SUMMARY OF PUBLIC COMMENTS AND RESPONSES ON THE PROPOSED REGULATION

A summary of the comments received during the initial public comment period from June 22, 2018 to August 30, 2018 that are relevant to this rulemaking is provided below, along with OEHHA's responses to those comments. Many commenters made the same or similar comments. This document does not provide an exhaustive accounting of all commenters addressing the same point.

A number of commenters expressed their support for the proposed regulation, including Anonymous 1, Anonymous 2, Bob L., CalChamber H8, Canteen H6, Clark, Cody, Coughlin, CRA H5, CSI, Eaton 1, Eaton 2, FDA, Glasser, HIKCC, Hornung, Hornung H7, Hotchkis, Industry Coalition, Kamangar, Lilla, Miller, Mountanos, NAMA/CAVC H9, NCA, NCA H2, NCA H3, NCA H4, NConfA, Philz, SCA and Tim J.

OEHHA acknowledges these comments.

Section 1. Legal or Procedural Issues

Authority

Comment 1 (CERT[12]): The proposed regulation exceeds OEHHA's statutory authority to adopt regulations.

Response 1: Proposition 65 authorizes OEHHA to "adopt and modify regulations… as necessary to conform with and implement [Proposition 65] and to further its purposes."[13] The proposed regulation furthers the statute's purpose by avoiding cancer warnings for exposures that do not pose a significant risk of cancer.

Proposition 65 states, "No person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual, except as provided in Section 25249.10."[14] This statutory language anticipates that individuals will receive warnings prior to being exposed to chemicals known to cause cancer or reproductive toxicity. However, the last clause of the Proposition 65 warning requirement section ("except as provided in Section 25249.10") provides a critical qualifier. Health and Safety Code section 25249.10(c) exempts from the warning requirement "exposure[s] for which the person responsible can show that the exposure poses no significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer…."[15] Accordingly, warnings are not required to be given for exposures to carcinogens if the exposure poses no significant risk of cancer. The proposed regulation furthers this purpose.

OEHHA has a long history of adopting regulations to further the purposes of the statute by avoiding unnecessary warnings for exposures to listed chemicals that pose no significant risk of cancer. It has adopted No Significant Risk Levels ("NSRLs") for more than 275 listed carcinogens that establish exposure levels that do not require a warning.[16] Courts have recognized that making the distinction between exposures that require a warning and those that do not is within OEHHA's authority and expertise.[17]

Similarly, OEHHA's predecessor entity adopted a regulation that exempts from the Proposition 65 warning requirement exposures to listed chemicals that are naturally occurring in food, which the Court of Appeal upheld in *Nicolle-Wagner v. Deukmejian*

[12] CERT 19, p. 3
[13] Health and Safety Code section 25249.12(a).
[14] Health and Safety Code Section 25249.6.
[15] There is a counterpart exemption for exposures to reproductive toxins, which is not relevant here.
[16] See Cal. Code Regs., tit. 27, § 25705.
[17] See *Mateel Envtl. Justice Found. v. OEHHA* (2018) 24 Cal.App.5th 220, 229.

(1991) 230 Cal.App.3d 652, 661. In upholding the naturally occurring regulation, the *Nicolle-Wagner*[18] court highlighted the importance of limiting warnings to only those exposures posing a significant risk:

> "This exemption, therefore, will further the statutory purpose in safeguarding the effectiveness of warnings which are given, and in removing from regulatory scrutiny those substances which pose only an 'insignificant risk' of cancer or birth defects within the meaning of the statute."

Moreover, like the proposed regulation here, the naturally occurring regulation does not name the listed chemicals it applies to, nor did the agency conduct a chemical-by-chemical risk assessment for exposures covered by the regulation. Furthermore, the naturally occurring regulation applies to chemicals in food regardless of whether safe harbor levels have been established for those chemicals. Neither the naturally occurring regulation nor the proposed regulation change or conflict with NSRLs that have been adopted for particular chemicals and have application outside of the scope of the two regulations.

Other examples of regulations OEHHA has adopted to further the purpose of the statute by addressing the need to require warnings or exempting from the warning requirement certain exposures to listed carcinogens include sections 25502 (listed chemicals in drinking water), 25503 (listed chemicals in water), and 25504 (listed chemicals in air). As with the proposed regulation, these regulations do not specifically name the chemicals they are intended to cover, and they apply equally to individual chemicals as well as mixtures of chemicals that may occur in the media identified in the regulation (i.e., food, water, air). The regulations specifically provide that "[n]othing in this article shall preclude a person from using evidence, standards, risk assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure to a listed chemical poses no significant risk."[19]

The proposed regulation also furthers the statutory purpose of Proposition 65 by addressing the lack of carcinogenicity of a mixture of chemicals, i.e., coffee.[20] A number of complex chemical mixtures are listed as carcinogens under Proposition 65, including alcoholic beverages, tobacco smoke, diesel engine exhaust, emissions from combustion of coal, marijuana smoke, analgesic mixtures containing phenacetin, and

[18] *Nicolle-Wagner*, 230 Cal.App.3d 652, at 661.
[19] Cal. Code Regs., tit. 27, § 25701(a).
[20] A chemical mixture is simply a substance comprised of chemicals. See: Rennie, R.&Law, J. (Eds.) 2016. *A Dictionary of Chemistry*. Oxford University Press: "Mixture: A system of two or more distinct chemical substances. Homogeneous mixtures are those in which the atoms or molecules are interspersed, as in a mixture of gases or in a solution. Heterogeneous mixtures have distinguishable phases, e.g. a mixture of iron filings and Sulphur. In a mixture there is no redistribution of valence electrons, and the components retain their individual chemical properties. Unlike compounds, mixtures can be separated by physical means (distillation, crystallization, etc.)."

MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture).[21] The carcinogenicity determination was primarily based on evidence for the carcinogenicity of the mixtures themselves, rather than for the individual chemicals comprising the mixtures. These chemical mixtures all contain known carcinogens, but not every chemical has been separately identified or analyzed as to their carcinogenicity. Given that OEHHA lists chemical mixtures that meet the statutory criteria for listing a known carcinogen and require a Proposition 65 warning, it follows that OEHHA has the authority to identify chemical mixtures containing listed chemicals that do not pose a significant risk of cancer and do not require a warning under Proposition 65.

No changes to the proposed regulation were made based on this comment.

Intent of Proposition 65

Comment 2 (CERT[22]): The voters wanted warnings for things like coffee. Decaffeinated coffee processed with methylene chloride was given as an example of a product that might need a warning by one of the initiative's authors, and also the principle opposition group against Proposition 65.

> "Since pre-election materials of both proponents and opponents of Proposition 65 stated that it would apply to decaffeinated coffee (a roasted coffee product), it is clear that the Voters intended Proposition 65 to apply to carcinogens in coffee"[23].

Response 2: Methylene chloride that is present in decaffeinated coffee as a result of processing is not a chemical "created by and inherent in the processes of roasting coffee beans or brewing coffee," and therefore is outside the scope of the proposed regulation. Residual methylene chloride in decaffeinated coffee is a synthetic chemical contaminant. As stated in the ISOR at page 12:

> "This regulation does not address exposures to listed chemicals in coffee that may occur if the chemicals are intentionally added to the coffee mixture or enter the mixture as contaminants through a means other than the inherent process of roasting coffee beans or brewing coffee."

Consequently, methylene chloride and other listed chemicals that are not formed in coffee through the process of roasting or brewing coffee but are intentionally added to

[21] OEHHA has specific statutory authority and a ministerial duty to list both chemicals and "substances" under Proposition 65: see Health and Safety Code section 25249.8(a) which incorporates Labor Code section 6382(b)(1), Title 27., Cal Code of Regs, section 25904(b) and *Chamber of Commerce v Brown* (2011) 196 Cal.App.4th 233, 126 Cal.Rptr.3d 214. Several chemical mixtures have been listed under this authority including alcoholic beverages.
[22] CERT H1, transcript p. 36; CERT 18, p. 5; CERT 19, p. 9
[23] CERT 19, p. 9

or enter coffee through other means are not exempt from warning requirements under the proposed regulation.

Nothing in the referenced sections of the voter materials indicates that voters intended there to be warnings on coffee that would be affected by this regulation.

No changes to the proposed regulation were made based on this comment.

Comment 3 (CSPI[24]): The proposed regulation runs counter to the right-to-know intent of Proposition 65 because it fails to warn consumers about chemicals known to the state to cause cancer.

Response 3: As discussed in the response to Comment 1, the proposed regulation furthers the purpose of Proposition 65 because the warning requirement does not apply to exposures to listed carcinogens that pose no significant risk of cancer to the average consumer[25].

No changes to the proposed regulation were made based on this comment.

Comment 4 (Bayard[26]): The proposed regulatory language, which declares that all the Proposition 65 carcinogens produced as part of the coffee roasting or brewing process have no significant risk, is contrary to both the letter and the intent of Proposition 65.

Response 4: As discussed in the response to Comment 1, the proposed regulation furthers the purpose of Proposition 65 because the warning requirement does not apply to exposures to listed carcinogens that pose no significant risk of cancer to the average consumer. OEHHA's determination that exposures to listed chemicals in coffee that are created as part of the roasting or brewing processes pose no significant risk of cancer is strongly supported by the extensive research evaluated and summarized by IARC and by OEHHA's evaluation of the IARC Monograph and studies published subsequent to the IARC review (See Section III). As explained in the ISOR (pp. 5-6) for this proposed regulation:

> "After reviewing more than 1000 studies of coffee and cancer, IARC concluded that there was inadequate evidence for the carcinogenicity of drinking coffee, and placed coffee in Group 3: "Not classifiable as to its carcinogenicity to humans". At the same time, IARC concluded that drinking coffee is inversely associated with cancers of the liver and uterine endometrium (i.e., risk is reduced). In

[24] CSPS, p. 2
[25] Health and Safety Code, section 25249.10(c); Title 27, Cal. Code of Regs., section 25721
[26] Bayard, pp. 2-5

> addition, IARC found moderate evidence of an inverse association (risk reduction) between coffee drinking and colorectal adenoma, a precursor lesion for most colorectal cancers, and also reported that studies either showed no association or a statistically significant inverse association for coffee intake and breast cancer. IARC also found that there is evidence suggesting lack of carcinogenicity for cancers of the pancreas and prostate, noting that "studies conducted worldwide consistently indicated no increased risk of prostate cancer associated with coffee drinking, with inverse or null associations observed in all studies". IARC concluded there was inadequate evidence of an association between coffee drinking and other types of cancers. IARC also found strong evidence in humans that coffee has antioxidant effects, effects that are related to reductions in cancer risk.
>
> "IARC's findings on coffee were based on its review of more than 1000 studies in humans, animals, in vitro and other experimental systems. The evaluation included numerous well-conducted prospective cohort and population-based case-control studies. IARC also evaluated several long-term studies of the carcinogenicity of coffee in rats and mice, and concluded that these studies provided inadequate evidence for the carcinogenicity of coffee." (internal citations omitted)

Further discussion regarding OEHHA's determination that listed chemicals in coffee pose no significant risk is provided throughout this FSOR, see for example responses to Comment 15.

No changes to the proposed regulation were made based on this comment.

Establishment of NSRLs and Calculation of Risks for Chemicals in Coffee

Comment 5 (CERT[27]): Based upon the following provision of the agreement in *AFL-CIO v Deukmejian*, (Sacramento County Superior Court case number 502541, settlement December 23, 1992), OEHHA cannot adopt the proposed regulation because it does not establish a numeric "no significant risk level" for every listed chemical in coffee.

Response 5: The paragraph in the settlement agreement referenced in the above comment reads as follows:

> "Defendants agree that any provision which is adopted after the date of this agreement to define the term "no significant risk" of the Act for any food, drug,

[27] CERT H1, transcript pp. 37-38; CERT 18, p. 5; CERT 19, p. 24

> cosmetic or medical device product, *and which employs standards derived from existing state or federal law* shall be based upon specific numeric standards for the chemical, as evidenced by the rulemaking file. Such level shall be consistent with and conform to sections 12703 [now 25703 Quantitative Risk Assessment] and 12721 [now 25721 Level of Exposure to Chemicals Causing Cancer] of title 22 [now 27] of the California Code of Regulations." (emphasis added)

The quoted paragraph from the trial court settlement in *AFL-CIO v Deukmejian* lacks any precedential value and in any event does not apply to this regulatory action. The proposed regulation does not employ "standards derived from existing state or federal law" when establishing a level of a chemical that poses no significant risk. Thus, to the extent the settlement continues to be binding on OEHHA, the proposed regulation does not implicate or violate it.

This comment also presumes that OEHHA must analyze coffee by determining on a chemical-by-chemical basis whether each exposure exceeds the safe harbor, if any. Since the proposed regulation applies to the combination or mixture of chemicals in coffee and determines, based on the science, that, taken as a whole, the chemicals formed through the roasting and brewing process do not pose a significant risk of cancer, it follows that none of the individual listed chemicals pose such a risk when combined and consumed in the mixture.

It should also be noted that OEHHA can modify or repeal the regulation if the scientific evidence that serves as the basis for the regulation changes at some point in the future. Science is not static and neither are OEHHA's regulations. As a scientific agency, OEHHA carefully monitors scientific developments in relation to its programs to ensure they reflect the current state of the science and will continue to do so. Additionally, any interested person can petition OEHHA to modify or repeal the regulation based on changes in the science or otherwise pursuant to Gov. Code section 11340.7.

No changes to the proposed regulation were made based on this comment.

Comment 6 (NCA[28]): The proposed regulation is the practical equivalent of a finding that the "no significant risk level" for carcinogens in coffee that are produced as part of and inherent in the processes of roasting and brewing coffee is infinite (NCA).

Response 6: Because the comment is not an objection or recommendation directed at the proposed action, it does not require a response. However, the proposed regulation does not establish a "no significant risk level" for the listed carcinogens in coffee.

[28] NCA, pp. 5-6

No changes to the proposed regulation were made based on this comment.

Comment 7 (Bayard[29]): OEHHA should perform its own quantitative risk assessment for each of the carcinogens in coffee.

Response 7: OEHHA disagrees that it must perform a quantitative risk assessment of the particular combination of chemicals in coffee, or focus on each listed chemical in coffee. OEHHA's determination that exposures to listed chemicals in coffee that are created as part of the roasting or brewing processes pose no significant risk of cancer is strongly supported by the extensive research evaluated and summarized by IARC and by OEHHA's evaluation of the IARC Monograph and studies published subsequent to the IARC review (See Section III). This determination and the proposed regulation are within OEHHA's authority as the lead scientific agency for Proposition 65 implementation, and, as discussed above, are consistent with other OEHHA regulations.

Moreover, there is no requirement in the statute for OEHHA to perform a quantitative risk assessment when it adopts a regulation pursuant to its authority under Health and Safety Code section 25249.12(a), and the commenter cited none. Adopting a regulation, as OEHHA is doing here, is to be distinguished from a situation in which the defendant in an enforcement action seeks to establish the statutory affirmative defense that the "exposure for which the person is responsible" poses no significant risk of cancer. (Health and Safety Code, section 25249.10(c).) In *Consumer Cause, Inc. v. SmileCare,* (2001) 91 Cal.App.4th 454, 476-477, for instance, the court held that a defendant failed to meet its burden to establish a safe-harbor affirmative defense in part because it failed to submit evidence concerning the level of exposure in question and did not establish the no-observable-effect level for mercury, which, in any event, is only relevant to establishing the safe-harbor defense for a reproductive toxicant. Similarly, in Phase I of the *CERT v. Starbucks* litigation, the trial court found that the defendants failed to establish the NSRL defense to the requirement to post warnings for acrylamide in coffee because they did not perform a quantitative risk assessment for acrylamide. (Statement of Decision on Trial (Phase I) (June 25, 2015), at p. 12, ¶ 42.) Establishing a safe harbor defense to the cancer warning requirement is different from OEHHA's task here. OEHHA is not adopting an NSRL. Instead, in furtherance of Proposition 65's purpose and intent not to require unnecessary cancer warnings, OEHHA is establishing a new regulation based on extensive scientific evidence concerning a particular consumer exposure to listed carcinogens in a food product, coffee, which OEHHA has determined poses no significant risk of cancer. The standard applicable to OEHHA's rulemaking is that the agency has not acted in a manner that is "arbitrary, capricious, or entirely lacking in evidentiary support." (*Exxon Mobil Corp. v. OEHHA* (2009) 169

[29] Bayard, p. 3

Cal.App.4th 1264, 1277 (internal quotations omitted).) A quantitative risk assessment is not required to support this rulemaking.

That is not to say that the statutory defense in section 25249.10(c), is irrelevant to this rulemaking. As discussed, it demonstrates the statutory purpose of avoiding warnings for exposures that do not pose a significant risk of cancer. It also furthers the statutory purpose that determinations of no significant risk are based on scientific evidence and standards. (Cf. *Consumer Cause, Inc. v. Smilecare*, *supra*, 91 Cal.App.4th at p. 470 [dentist's declaration stating that dental amalgam fillings containing the reproductive toxicant mercury are "safe" was not sufficient to support the statutory defense].) The proposed regulation furthers both of these purposes, and is therefore within OEHHA's authority.

No changes to the proposed regulation were made based on this comment.

Promulgation of Other Regulations for Chemicals in Food

Comment 8 (Industry Coalition; NConfA[30]): An IARC monograph should not be a prerequisite for OEHHA to promulgate similar regulations regarding food or beverage items in the future and, instead, similar actions should continue to be based on the weight of the evidence approach.

Response 8: Because the comment is not an objection or recommendation directed at the proposed action, it does not require a response. However, OEHHA has not stated that an IARC monograph is a prerequisite for OEHHA to promulgate similar regulations, although in this case the IARC monograph played a significant role in OEHHA's consideration of the extensive scientific evidence that supports its action.

No changes to the proposed regulation were made based on this comment.

Proposition 65 Listings

Comment 9 (CSPI[31]): OEHHA should carefully review evidence suggesting maternal coffee consumption is linked to reproductive problems and harm to fetuses and children, including low birth weight, preterm birth, pregnancy loss and childhood leukemia, and consider providing clear and reasonable advice to pregnant women before finalizing its proposal on coffee.

Response 9: With regard to non-cancer effects of coffee consumption such as low birth weight, this comment is beyond the scope of the proposed regulation, which only

[30] Industry Coalition, pp.1-2; NConfA, pp. 2-4
[31] CSPI, p. 5

addresses exposures to listed chemicals formed in coffee during the roasting/brewing process. With regard to childhood leukemia resulting from maternal coffee drinking, OEHHA disagrees with the commenter's assessment of the scientific evidence. See responses to Comments 46-49 below.

No changes to the proposed regulation were made based on this comment.

Comment 10 (CSI; Eaton 1; Eaton 2; Tim J.): Coffee should be removed from the Proposition 65 list or coffee should not be added to the list.

Response 10: Coffee is not a listed substance under Proposition 65, nor does this regulation propose adding coffee to the list. The proposed regulation addresses exposures to listed chemicals formed by roasting coffee beans or brewing coffee that are present in coffee[32]. Proposition 65's warning requirements apply to consumer products[33]. Therefore, OEHHA's proposed regulation applies to exposures to listed chemicals from consumption of coffee, which is a consumer product, even though coffee itself is not listed.

No changes to the proposed regulation were made based on this comment.

Implications of 2013 Amendments to Proposition 65

Comment 11 (CERT[34]): OEHHA's discussion of the *CERT v Starbucks* case in the ISOR for the proposed regulation is an attempt to make the regulation operate retroactively, which is contrary to the Legislature's intent to require coffee warnings prospectively when it amended Proposition 65 in 2013.

Response 11: OEHHA disagrees with the commenter that the Legislature intended to require coffee warnings prospectively when it amended Proposition 65 in 2013 to provide a cure provision for certain Proposition 65 violations associated with failure to post warnings on food or beverages (Health and Safety Code, 25249.7(k)). The 2013 amendments do not mention coffee and take no position that any specific food or

[32] See definition in ISOR for this proposed regulation:
"Coffee," as referenced in this document and the proposed regulation, refers to a beverage made by percolation, infusion, or decoction from the roasted seeds of a coffee plant. Coffee is a unique and complex chemical mixture that contains numerous chemicals formed during the roasting of coffee beans. Chemicals are also formed during the brewing of coffee. Among the chemicals formed during these processes are a number of carcinogens listed under Proposition 65 (e.g., acetaldehyde, acrylamide, benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, chrysene, dibenz(a,h)anthracene, formaldehyde, furan, furfuryl alcohol, indeno(1,2,3-cd)pyrene, 4-methylimidazole, naphthalene, and pyridine). Coffee also contains numerous compounds that either exhibit or are considered to have cancer chemopreventive properties (e.g., free radical scavengers, antioxidants). (internal citations omitted).
[33] Committee of Dental Amalgam Manufacturers and Distributers v. Stratton,(9th Circuit, 1996) 92 F.3d 807
[34] CERT 19, pp. 10-11

beverage (other than alcoholic beverages, which are listed) requires a warning. Nothing in these amendments precludes OEHHA from making conclusions about cancer risks from any specific food or beverage, in this case coffee.

Additionally, in adopting the proposed regulation, OEHHA expresses no view on the *Starbucks* ruling that the coffee companies failed to establish an affirmative defense to the warning requirement or on whether the court reached the right result based on the issues and evidence presented in the case. The *Starbucks* case is not final and all appeals have not been exhausted, so no rulings or orders from that case have precedential effect. Nor is OEHHA a party to that case.

No changes to the proposed regulation were made based on this comment.

Other Concerns

Comment 12 (CERT[35]): No one at OEHHA read the IARC Monograph before the Initial Statement of Reasons was published.

Response 12: This comment does not constitute an objection or recommendation to the proposed regulation. Moreover, the commenter is incorrect. OEHHA carefully read the IARC Monograph and cited IARC's findings on the carcinogenicity of drinking coffee throughout the ISOR. In addition, OEHHA was aware of the IARC findings since 2016 when an article summarizing the findings and previewing the extensive analysis and compilation of studies in the Monograph was published in the medical journal Lancet Oncology[36].

No changes to the proposed regulation were made based on this comment.

Comment 13 (CERT; Melnick[37]): In the section "Preliminary Comments", CERT laid out its interest in the proposed regulation, made comments about its ongoing litigation on acrylamide in coffee, stated that the coffee industry can easily reduce acrylamide levels in roasted coffee, as did Dr. Melnick, and noted that the European Commission regulates acrylamide in coffee. Additionally, both commenters stated that OEHHA should support the development and implementation of methodologies that reduce this genotoxic carcinogen in coffee to levels below its NSRL.

[35] CERT H1, transcript p. 25
[36] Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Mattock H, Straif K, on behalf of the International Agency for Research on Cancer Monograph Working Group (2016). Carcinogenicity of drinking coffee, mate, and very hot beverages. *Lancet Oncol* 17:877-878. Available at: http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(16)30239-X.pdf
[37] CERT H1, transcript p. 19; CERT 18, pp. 6-9, 228; Melnick, pp. 5, 9-11

Response 13: These comments are outside the scope of this rulemaking. The proposed regulation does not prevent the development and implementation of methodologies that can reduce the acrylamide formed during the roasting of coffee beans or the brewing of coffee. OEHHA acknowledges that the European Commission regulates[38] acrylamide levels in coffee. The study results reported in the IARC Monograph do not show that acrylamide reductions affect the lack of evidence for the carcinogenicity of coffee consumption.

No changes to the proposed regulation were made based on this comment.

Comment 14 (FDA): FDA[39] supports the proposed regulation. It agrees with OEHHA that the most current research on coffee and cancer does not support a Proposition 65 cancer warning for coffee. FDA contends that such a warning would be misleading to consumers. It also notes that FDA has previously expressed concerns about Proposition 65 cancer warnings for foods when those warnings are based on the presence of acrylamide. Thus, according to the comment letter, a cancer warning on coffee would render the product misleading under federal law and could lead to preemption.

Response 14: Although the FDA's comment is not a formal expression of federal policy, OEHHA appreciates FDA's support for the proposed regulation. To the extent the FDA believes that Proposition 65 warnings on coffee would conflict with federal law, the proposed regulation will avert this potential issue because no warning would be required for the exposures to listed chemicals covered by the regulation.

Section II. General Scientific Issues

IARC Hazard Findings

Comment 15 (CERT; Smith; CSPI[40]): OEHHA relies on the IARC Monograph conclusion that coffee poses no significant cancer risk but IARC does not quantify cancer risk, and the Monograph is instead a qualitative hazard evaluation on whether coffee is capable of causing cancer. OEHHA misinterpreted and mischaracterized IARC's conclusions. IARC did not conclude that coffee consumption has been proven to be "safe" or that it does not increase the risk of any human cancer. "Although the IARC's classification of coffee 'is not a determination of non-carcinogenicity or overall safety,' OEHHA appears to interpret IARC's conclusion as meaning that coffee does not

[38] European Commission (2017), p. 21, Annex IV. Commission Regulation (EU) 2017/2158 of 20 November 2017 establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in food (Text with EEA relevance.) Available at: https://eur-lex.europa.eu/eli/reg/2017/2158/oj
[39] Susan T. Mayne, Ph.D. Director, Food and Drug Administration, Center for Food Safety and Applied Nutrition
[40] CERT 18, pp. 13-15, 24-28, 43, 63, 181-216; Smith, pp. 2-3; CSPI, pp. 4-5

cause human cancer and is safe…Had IARC concluded that consumption of coffee does not cause human cancer, IARC would have classified coffee in Group 4 rather than Group 3." IARC monographs are considered authoritative for identifying cancer hazard, "but they are clearly not reliable matter for determining risks" (CERT 18, p. 15), and they are not a quantitative risk assessment.

Response 15: The proposed regulation does not state that coffee is safe. Instead, OEHHA's conclusion, based on its review of the IARC Monograph, is that exposure to listed chemicals in coffee created from roasting coffee beans or brewing coffee does not pose a significant risk of cancer.

IARC has categorized only one agent as Group 4: "Probably not carcinogenic to humans."[41] Rather, as noted in the ISOR on page 5, IARC concluded there is "inadequate evidence in humans for the carcinogenicity of drinking coffee"[42], and placed coffee in Group 3: "Not classifiable as to its carcinogenicity to humans". In addition, IARC found "evidence suggesting lack of carcinogenicity of coffee drinking in humans for cancers of the pancreas, liver, female breast, uterine endometrium, and prostate" and "inverse associations with drinking coffee" for "cancers of the liver and uterine endometrium". OEHHA's conclusions are based on IARC's review of the large volume of epidemiology data available on more than 20 cancer sites in humans[43].

OEHHA agrees with the commenters that IARC monographs are authoritative for identifying cancer hazard, and they are not a quantitative risk assessment. The available scientific information, including the 2018 Monograph on Drinking Coffee by the International Agency for Research on Cancer (IARC)[44], supports OEHHA's determination that exposures to listed chemicals in coffee created by roasting coffee beans or brewing coffee do not pose a significant risk of cancer for purposes of Proposition 65. The weight of the evidence from the very large number of studies in the scientific literature does not support an association between the complex mixture of chemicals that is coffee and significant risk of cancer to the average consumer. OEHHA's key overall considerations in adopting this regulation are as follows:

[41] The finding for the chemical – caprolactam -- was reported in 1987 [IARC (1987). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7, p. 59, World Health Organization, Lyon, France. Available at https://monographs.iarc.fr/wp-content/uploads/2018/06/Suppl7.pdf], and 1999 [IARC (1999). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 71. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. World Health Organization, Lyon, France. Available at: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-50/ . In 2019 caprolactam was moved to Group 3 (not classifiable as to its carcinogenicity to humans) following the 2019 update to the IARC Monographs preamble (see Agents Classified by the IARC Monographs Volumes 1-123 (IARC, 2019), available at: https://monographs.iarc.fr/wp-content/uploads/2018/09/ClassificationsAlphaOrder.pdf).
[42] IARC (2018), full citation provided in footnote 3, p. 425.
[43] IARC (2018), full citation provided in footnote 3, p. 33.
[44] IARC (2018), full citation provided in footnote 3.

- There is “inadequate evidence” in a very large number of human studies for the carcinogenicity of drinking coffee[45].
- There are inverse associations indicative of protective effects with drinking coffee for human cancers of the liver and uterine endometrium[46].
- There is “inadequate evidence” of increased carcinogenicity in animals administered coffee in controlled experiments[47].
- There are inverse associations in a number of animal experiments and the overall evidence from animal studies is that of reduced incidence or multiplicity of cancers with coffee intake[48].
- There is a rich mix of cancer-preventative agents in brewed coffee[49].

Taken together, these factors provide the basis for OEHHA’s determination that exposure to listed carcinogens in coffee that are created as part of and inherent in the processes of roasting and brewing does not pose a significant cancer risk for purposes of Proposition 65.

No changes to the proposed regulation were made based on this comment.

Comment 16 (Melnick; CERT[50]): Commenters state that it does not appear that criteria to draw the conclusion that there is evidence suggesting lack of carcinogenicity (as IARC did for five sites: pancreas, liver, female breast, uterine endometrium, and prostate) have been adequately met and fully characterized in the IARC Monograph on coffee.

Response 16: OEHHA disagrees with the comment. OEHHA did not find any evidence that IARC applied its criteria improperly in evaluating the epidemiological evidence in the coffee Monograph.

IARC lays out general criteria used for evaluating epidemiological studies for lack of evidence of carcinogenicity in the preamble of each Monograph. These criteria are provided in a single paragraph but we have listed them out here and assigned them numbers for ease of reference.

[45] Explained on p.12 of the ISOR as “a lack of evidence showing increases in cancers”. See also p. 11 of the ISOR: “[coffee] has not been found to increase the risk of any cancers” (citing p. 425 of 2018 IARC Monograph).
[46] Explained on p. 12 of the ISOR as “reductions of specific cancers resulting from coffee drinking”. See also p. 11 of the ISOR: “[coffee] is associated with reduced risk of some cancers” (citing p. 425 of 2018 IARC Monograph).
[47] IARC (2018), full citation provided in footnote 3, p. 425
[48] IARC (2018), full citation provided in footnote 3, pp. 335-352, 420-421
[49] ISOR pp. 7-10
[50] Melnick, p. 8; CERT 18, pp. 170-172

1. “When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity.”
2. “Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above [in the Preamble]. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty.”
3. “In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk [RR] that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size.”
4. “Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure."
5. “Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.”

For each epidemiologic study reviewed in the IARC Monograph on coffee, strengths, limitations, and notable characteristics are described, for example, the lack of control for an important confounder. IARC’s discussion of the evidence in humans for each cancer site includes thorough explanations of potential biases and confounding. The IARC Monograph’s *Section 5. Summary of Data Reported* explains the basis for the conclusion that there is evidence suggesting lack of carcinogenicity for each of these five cancer sites (pp. 416-418).

Pancreas:

IARC found a number of human studies on cancer of the pancreas and drinking coffee for consideration[51]. IARC discusses these studies on pages 144-176 of the Monograph, with results tabulated (Tables 2.3 and 2.4 of the Monograph). “Cohort studies and population-based case–control studies, adjusting for multiple confounders, showed no overall association with total coffee drinking or with decaffeinated coffee drinking.” The summary also emphasized consistent null findings in large methodologically sound

[51] As noted in the Preamble to the IARC Monograph Volume 116 (p. 12): “ Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description. The reasons for not giving further consideration to an individual study also are indicated in the square brackets.”

studies. A meta-analysis IARC reported on as rigorous found a summary relative risk[52] of 1.00 for cohort studies, with a narrow 95% confidence interval [CI] (0.95-1.05)[53]. When combining case-control studies that were not adjusted for smoking, the authors estimated a weak positive finding, which IARC attributed to residual confounding by smoking.

The overall results of IARC's evaluation of the epidemiological evidence on coffee drinking and pancreatic cancer are summarized on pages 416-417 of the Monograph:

> "Evidence of the association between coffee drinking and cancer of the pancreas was available from 20 cohort studies and 22 case-control studies that controlled for smoking, of which 14 were population-based and 8 hospital-based. The review of epidemiological studies was restricted to those that adjusted for smoking. Cohort studies and population-based case–control studies, adjusting for multiple confounders, showed no overall association with total coffee drinking or with decaffeinated coffee drinking. The most important set of studies on which this conclusion is based is a pooled[54] analysis of cohort studies with comparable methodology which found no association, including in non-smokers. A high-quality meta-analysis also showed no association with coffee intake in cohort studies or in case–control studies that adjusted for smoking. Several large cohort studies published after this meta-analysis similarly found null associations. Overall, based on many large studies, there is no evidence of an association between coffee drinking and risk of pancreatic cancer." [notation added]

Liver:

IARC found a number of human studies on cancer of the liver and drinking coffee for consideration, and described these studies on pages 176-204 of the Monograph, with results tabulated. Table 2.5 in the Monograph shows that none of the 14 cohort studies and Table 2.6 shows that none of the 11 case-control studies found a statistically significant positive association between coffee drinking and increased liver cancer. The discussion and tabulation shows attention to bias and confounding issues. Meta-analyses reviewed by the working group reported relatively strong protective effects, with the upper confidence bounds on the relative risks less than one.

[52] A relative risk of 1.0 indicates that, all other things being equal, people drinking coffee are as likely to develop pancreatic cancer as those that do not. The 95% confidence interval is the result of a statistical analysis in essence indicating 95% confidence that the actual value for the relative risk falls between the range in the interval.
[53] Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C et al. (2012). A meta-analysis of coffee consumption and pancreatic cancer. *Ann Oncol*. 23(2):311–8.
[54] Pooled analysis involves combining the raw data from multiple individual studies and reanalyzing it. See e.g., Greenland S and O'Rourke K (2008). Meta-analysis, Chapter 33. In: Rothman KJ, Greenland S, Lash TL editors. *Modern Epidemiology* (3rd Edition). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, pp. 652–682.

The overall results of IARC's evaluation of the epidemiological evidence on coffee drinking and liver cancer are summarized on page 417 of the Monograph as follows:

> "A total of 14 cohort studies and 11 case–control studies conducted in Asia, Europe and North America examined the association between coffee consumption and the risk of cancer of the liver. All cohort studies adjusted for smoking and alcohol intake and, where possible, for hepatitis virus infection status and diabetes. All cohort studies observed inverse associations, which were statistically significant in most studies. Separate analyses by sex and by hepatitis C virus and/or hepatitis B virus infection status yielded similar results. Most case-control studies also observed inverse or null associations. In a 2015 pooling project of cohort studies in the USA (over 860 cases of hepatocellular carcinoma), the risk in the highest compared with the lowest category of coffee consumption was reduced by about 25%. The Working Group concluded that a consistent, statistically significant, inverse association between coffee drinking and risk of liver cancer has been observed in multiple studies."

Breast:

IARC found a number of human studies on cancer of the breast and drinking coffee for consideration, and described these studies on pages 204-241 of the Monograph, with results tabulated. Table 2.7 in the Monograph shows that none of the 23 cohort studies and Table 2.8 shows that only one of the 22 case-control studies found a statistically significant positive association between coffee drinking and increased breast cancer. The discussion and tabulation shows attention to bias and confounding issues. Meta-analyses reported by the working group reported null or protective effects with narrow confidence intervals.

The overall results of IARC's evaluation of the epidemiological evidence on coffee drinking and breast cancer are summarized on page 417 of the Monograph as follows:

> "Evidence of the association between coffee consumption and risk of cancer of the breast was available from 23 cohort and 22 case-control studies. Most of the reviewed studies showed no association, and several reported statistically significant inverse associations between coffee intake and breast cancer overall or among subgroups of premenopausal or postmenopausal women. The most recent meta-analysis of about one million women and more than 50 000 breast cancer cases reported a modestly decreased risk for the highest compared with lowest levels of coffee consumption, with an indication of an inverse dose–response relationship. Studies published after this meta-analysis reported null or inverse associations overall and among postmenopausal women. An inverse association was also

observed in the recent large cohort study (2016). Inverse associations were reported in a small number studies among women with *BRCA1* mutations. One population-based case–control study among non-carriers of *BRCA1/2* mutations reported a positive association."

Endometrium:

IARC found a number of human studies on cancer of the uterine endometrium and drinking coffee for consideration, and described these studies on pages 241-258 of the Monograph, with results tabulated. Table 2.9 in the Monograph shows that none of the 12 cohort studies and Table 2.10 shows that none of the eight case-control studies found a statistically significant positive association between coffee drinking and increased endometrial cancer. A number of studies showed inverse associations. The discussion and tabulation shows attention to bias and confounding issues. Meta-analyses reported by the working group showed protective effects.

The overall results of IARC's evaluation of the epidemiological evidence on coffee drinking and endometrial cancer are summarized on page 417 of the Monograph as follows:

"Evidence of the association between drinking coffee and risk of endometrial cancer was available from 20 informative studies (12 cohort and 8 case-control studies) where body mass index and smoking were taken into account. Evidence from four of the largest cohort studies (the Swedish Mammography Cohort, the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, the Nurses' Health Study (NHS) and NHS II, and European Prospective Investigation into Cancer and Nutrition (EPIC)) with over 6000 cases showed an inverse association with coffee drinking. The Million Women Study, including another 4000 cases, found a null association. Evidence from case-control studies is consistent with that of cohort studies, suggesting an inverse or a null association. A meta-analysis published in 2012 found a 30% lower risk of endometrial cancer among coffee drinkers, consistent with the majority of cohort and case–control studies."

Prostate:

IARC found a number of human studies on cancer of the prostate and drinking coffee for consideration, and described these studies on pages 258-280 of the Monograph, with results tabulated. Table 2.11 in the Monograph shows that none of the 10 tabulated cohort studies and Table 2.12 shows that none of the four case-control studies found a statistically significant positive association between coffee drinking and

increased prostate cancer. A number of studies showed inverse associations. The discussion and tabulation shows attention to bias and confounding issues. Recent meta-analyses discussed showed null or protective effects, with relatively narrow confidence bounds. Coffee showed protective effects for fatal prostate cancer in the meta-analyses.

The overall results of IARC's evaluation of the epidemiological evidence on coffee drinking and prostate cancer are summarized on pages 417-418 of the Monograph as follows:

> "Evidence from ten cohort studies and four case-control studies of the association between coffee drinking and cancer of the prostate was evaluated. The greatest weight was given to studies of aggressive and fatal prostate cancer to reduce the potential for bias from screening. No case-control or cohort studies found positive associations with the risk of total prostate cancer. Recent meta-analyses of cohort and case–control studies estimated inverse associations for fatal prostate cancer and no association for advanced prostate cancer. Studies conducted worldwide consistently indicated no increased risk of prostate cancer associated with coffee drinking, with inverse or null associations observed in all studies."

In reviewing the IARC criteria against the discussion and tabulations in the IARC Monograph, there was no indication of lack of attention by the IARC working group to the IARC criteria for any of the sites found to have evidence suggesting lack of carcinogenicity – pancreas, liver, female breast, uterine endometrium, and prostate.

1. For all sites, epidemiological studies showed little or no indication of an association between an exposure and cancer, consistent with the first criterion.
2. With regard to the second criterion, bias, confounding and misclassification of exposure or outcome was clearly considered for each of the sites.
3. Regarding the third criterion, pooled estimates of effect (e.g., relative risk) included unity with tight confidence bounds, except for cases where risk reduction was indicated, in which case the estimate fell below unity[55].
4. Regarding the fourth criterion, for studies of adequate quality, neither individual studies nor pooled results of all the studies show any consistent tendency that the relative risk of cancer increases with increasing level of exposure.
5. Regarding the fifth criterion, the cohorts reviewed had an adequate period of follow-up between prospectively collected data on coffee consumption and the occurrence of cancer. Only the cohorts deemed to have inadequate follow-up were signaled with a comment in the text and tables (e.g., for pancreatic cancer,

[55] Relative risks falling below unity means that coffee drinkers were less likely to develop the cancer than non-coffee drinkers, all other things being equal.

a short follow-up time was noted as a limitation of the study by Hiatt et al. (1988) on page 145 of the IARC Monograph).

No changes to the proposed regulation were made based on this comment.

Causation, Association, and Inverse Associations

Comment 17 (CERT; NCA[56]): Various comments questioned the validity of using observational epidemiology studies to make causal inferences:

- "All of the epidemiology studies that have investigated risks of cancer from coffee consumption are observational epidemiological studies or meta-analyses of such studies. However, such studies are wholly inadequate to determine causality."
- "Indeed the authors of epidemiologic studies acknowledge their studies do not establish causation".
- "Most statistical associations reported in observational epidemiological studies are not causal and it is especially difficult to conclude that associations regarding a single dietary component are causal, due to innumerable confounding factors in the diet, as well as innumerable non-dietary known and unknown confounding factors, as well as measurement error and innumerable other biases that plague observational epidemiology studies."
- "Even the most sophisticated epidemiology study design is incapable of determining causation. That is precisely why those who evaluate observational studies that associate exposures with human disease bend over backwards to avoid causal statements"… "The categories of likely causal, highly likely the exposure and the outcome are related (but not necessarily causal), uncertain relationship between exposure and outcome, etc. are deemed arbitrary. Artefactual is only one of many possible categories. Indeed, some prefer to see relationships between an exposure and an outcome along a continuum."

Response 17: An individual observational study can have clear evidentiary value in contributing to evidence for causality, even if definitive causal conclusions cannot be drawn from a single study. As noted by the Institute of Medicine[57]:

> "In an observational study, the investigator does not control exposure of the people in the study and does not intervene in any way in the population under study. Although observational studies may lack the comparability of exposed and non-exposed characteristic of controlled experiments, they are nonetheless capable of providing evidence about the relationship between exposure and

[56] CERT 18, pp. 37-39; CERT H1, transcript pp. 26-28; NCA, pp. 10-14
[57] Institute of Medicine (IOM 2008). Improving the presumptive disability decision-making process for veterans. Washington, DC: The National Academies Press, Chapter 7, page 153. Available at: https://www.nap.edu/download/11908

> health and are generally the only option available to obtaining human evidence of the effect of potentially harmful exposures."

Individual studies are then considered in the context of the body of epidemiological evidence. IARC, the Institute of Medicine[58], the federal National Toxicology Program, the US Environmental Protection Agency, and California's Carcinogen Identification Committee (the state's qualified experts for identifying carcinogens under Proposition 65) all review and weigh observational studies when evaluating a chemical or chemical mixture to make inferences about its potential to cause cancer. To facilitate drawing causal inferences, guidelines and criteria are used[59,60,61]. Such guidance usually includes evaluating the quality of individual studies, paying particular attention to design and study characteristics, weighing the overall evidence across human studies; taking into account bias, confounding, and looking at the evidence across studies, and ultimately integrating evidence from different data streams, i.e., findings from human epidemiology studies, results of animal experiments, and data from mechanistic studies, such as how the chemical or chemical mixture may operate on a molecular level to cause cancer.

To date, IARC has identified 120 agents as Group 1 Agents, as "carcinogenic to humans". This includes some substances in the diet like the mycotoxin aflatoxin B1. Many of the chemicals in Group 1 were identified because they have sufficient evidence of carcinogenicity in humans, *in toto* or in large part from observational human studies. A key consideration in making these determinations is whether bias, chance and confounding can be ruled out with reasonable confidence.

With regard to individual author conclusions from a single study, a key consideration in judging the evidence is the extent to which findings are repeated or seen in multiple studies and in different circumstances. For example, IARC notes in its Preamble[62]:

> "Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies."

[58] Now named the Health and Medicine Division within the National Academy of Sciences, Engineering and Medicine
[59] National Toxicology Program (NTP 2015), Handbook for Preparing Report on Carcinogens Monographs, US Department of Health and Human Services, June, 2015. Available at https://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf
[60] US Environmental Protection Agency (US EPA 2005). Guidelines for Carcinogen Risk Assessment, Chapter 2: Hazard Assessment, EPA/630/P-03/001F. Available at https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf
[61] IOM (2008), full citation provided in footnote 57. Chapter 8: Synthesizing the Evidence for Causation.
[62] IARC (2018), full citation provided in footnote 3, pp. 9-32.

Thus authors of an individual study may point out the extent to which their study contributes to observed trends but are typically not so presumptuous as to assert causal conclusions based on the findings in their particular study.

The IARC labels for human evidence focus on the sufficiency of evidence. The highest level of evidence is:

> "Sufficient evidence of carcinogenicity": "The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence."

The next category is:

> "Limited evidence of carcinogenicity": "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."

The next category is:

> "Inadequate evidence of carcinogenicity": "The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available."

Finally:

> "Evidence suggesting lack of carcinogenicity": "There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up."

In their carcinogenicity evaluations, the US Environmental Protection Agency and National Toxicology Program similarly categorize the human evidence.

In the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, there is no specific category with a label used solely for protective effects. In evaluating the evidence for carcinogenicity from human studies, the label "evidence suggesting lack of carcinogenicity" captures substances showing either lack of evidence of carcinogenicity or a protective effect. When overall the evidence suggests or shows a protective effect, a statement to that effect may be made in the narrative regarding risk reduction or an inverse association. However, the IARC Handbooks of Cancer Prevention Program evaluate substances and circumstances for preventive effects. In this Series, the evaluations result in ratings regarding the human evidence for preventive effects, e.g., "sufficient evidence of cancer-preventive effects", as well as for the overall evidence across the different data streams. Coffee has not been evaluated in the IARC Handbook series[63].

No changes to the proposed regulation were made based on this comment.

Comment 18 (CERT[64]): CERT raises issues related to whether the inverse associations for coffee and certain cancer sites OEHHA referred to in the ISOR are causal. For example:

> "The Initial Statement of Reasons selectively identifies some observational epidemiologic studies and meta-analyses of observational epidemiologic studies that report statistically significant decreased risks of certain cancers in association with consumption of coffee. However, the Initial Statement of Reasons does not address whether any of these associations are actually causal. This is a critical omission, because most statistical associations reported in observational epidemiological studies are not causal and it is especially difficult to conclude that associations regarding a single dietary component are causal, due to innumerable confounding factors in the diet, as well as innumerable non-dietary known and unknown confounding factors, as well as measurement error and innumerable other biases that plague observational epidemiology studies. Certainly, IARC has not made any such causal conclusion. Nor does OEHHA do so in its Initial Statement of Reasons. Critically, in the absence of any determination that any of the inverse associations reported in the observational epidemiologic studies of coffee and cancer are actually causal, it cannot be scientifically concluded that coffee does not cause cancer, let alone that it prevents cancer. Yet, this is what OEHHA appears to implicitly conclude in its Initial Statement of Reasons" (CERT 18, p. 48).

[63] International Agency for Research on Cancer (IARC 2017). Working Procedures of the *IARC Handbooks of Cancer Prevention*, World Health Organization, Lyon, France. Available at: http://handbooks.iarc.fr/workingprocedures/index.php

[64] CERT 18, pp. 37-39, 48-52; CERT H1, transcript pp. 24-26

Response 18: As noted in the response to comment 17, IARC does not have a category that distinguishes among items with the conclusory label "evidence suggesting lack of carcinogenicity" from those showing inverse relationships, namely protective effects. In the summary section of the IARC Monograph, the overall inverse associations between coffee drinking and cancers of the uterine endometrium and liver are clearly considered and described with respect to the IARC Preamble guidelines for evaluating causality.

For liver cancer, inverse associations were noted in both cohort and case-control designs, consistently across several geographic locations. Confounding by smoking and alcohol intake and, where possible, for hepatitis virus infection status and diabetes, was ruled out. (For a definition and discussion of confounding, see response to comment 21.)

For endometrial cancer, a number of informative cohort and case-control studies showed an inverse association with coffee drinking, consistently across several geographic locations. Potential confounding by body mass index (BMI) and smoking were ruled out.

The summary notes the following for cancers of the liver and uterine endometrium:

> *Liver:*
>
> "A total of 14 cohort studies and 11 case-control studies conducted in Asia, Europe and North America examined the association between coffee consumption and the risk of cancer of the liver. All cohort studies adjusted for smoking and alcohol intake and, where possible, for hepatitis virus infection status and diabetes. All cohort studies observed inverse associations, which were statistically significant in most studies. Separate analyses by sex and by hepatitis C virus and/or hepatitis B virus infection status yielded similar results. Most case–control studies also observed inverse or null associations. In a 2015 pooling project of cohort studies in the USA (over 860 cases of hepatocellular carcinoma), the risk in the highest compared with the lowest category of coffee consumption was reduced by about 25%. The Working Group concluded that a consistent, statistically significant, inverse association between coffee drinking and risk of liver cancer has been observed in multiple studies."[65]

[65] IARC (2018), full citation provided in footnote 3, p. 417.

Endometrium:

"Evidence of the association between drinking coffee and risk of endometrial cancer was available from 20 informative studies (12 cohort and 8 case-control studies) where body mass index and smoking were taken into account. Evidence from four of the largest cohort studies (the Swedish Mammography Cohort, the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study, the Nurses' Health Study (NHS) and NHS II, and European Prospective Investigation into Cancer and Nutrition (EPIC)) with over 6000 cases showed an inverse association with coffee drinking. The Million Women Study, including another 4000 cases, found a null association. Evidence from case–control studies is consistent with that of cohort studies, suggesting an inverse or a null association. A meta-analysis published in 2012 found a 30% lower risk of endometrial cancer among coffee drinkers, consistent with the majority of cohort and case-control studies."[66]

It is important to consider bias, confounding, and misclassification, and each cancer site and study were carefully evaluated by IARC to make a judgment regarding the observed results. Specifically, IARC explained the important confounders for coffee consumption and cancer risk in general (e.g., smoking) and for each cancer site (e.g., BMI for cancer of the endometrium[67]). Studies that did not control for important confounders were either excluded or given less weight in the overall evaluation. It is also important to consider the timing between exposure and outcome. IARC noted that studies in which sensitivity analyses were conducted that excluded patients diagnosed too close to the start of the cohort were considered to be the most informative. Studies assessing dietary exposures can be susceptible to recall bias. Patients with cancer may change their coffee drinking habits, which can lead to bias in the analyses. IARC noted possible biases and other key study limitations in square brackets.

OEHHA notes the IARC findings of inverse associations for the liver and uterus are consistent with the US Food and Drug Administration and the joint World Cancer Research Fund and American Institute for Cancer Research reviews. These reviews, conducted by expert panels, evaluated the evidence of health effects and coffee and made formal conclusions regarding both protective and harmful cancer effects. The panels concluded that coffee has or is likely to have protective effects for certain sites and, similar to IARC, they have not found coffee to increase cancer risk.

[66] IARC (2018), full citation provided in footnote 3, p. 417.
[67] IARC (2018), full citation provided in footnote 3, p. 241.

The US Food and Drug Administration's Dietary Guidelines Advisory Committee concluded[68]:

> "… moderate coffee consumption can be incorporated into a healthy dietary pattern, along with other healthful behaviors".
>
> "Strong and consistent evidence shows that consumption of coffee within the moderate range (3 to 5 cups/d or up to 400 mg/d caffeine) is not associated with increased risk of major chronic diseases, such as cardiovascular disease (CVD) and cancer and premature death in healthy adults…In addition, consistent observational evidence indicates that regular consumption of coffee is associated with reduced risk of cancer of the liver and endometrium, and slightly inverse or null associations are observed for other cancer sites."

The systematic review of various dietary constituents and other modifiable risk factors and cancer conducted by the World Cancer Research Fund and American Institute for Cancer Research in its Continuous Update Project expert panel[69] found there is

> "strong evidence that"… "coffee DECREASES the risk of liver cancer and endometrial cancer".

The review also found "limited evidence" of a suggestive decreased risk of cancers of the mouth, larynx, and pharynx and of cancers of the skin. Finally, it noted regarding the liver and endometrium that:

> "Coffee is rich in a large number of bioactive compounds including caffeine, chlorogenic acids and numerous phenolic compounds. Emerging evidence suggests that these compounds may have beneficial effects on the liver ranging from antioxidant, anti-inflammatory properties to the inhibition of angiogenesis, but the main underlying mechanisms of the role of coffee in liver cancer development are not fully elucidated. Coffee is also associated with improved insulin sensitivity, decreased incidence of metabolic syndrome and reduced level of liver injury, which could represent additional mechanisms by which coffee drinking may reduce the risk of liver cancer development."

[68] Dietary Guidelines Advisory Committee (DGAC 2015). Scientific Report of the 2015 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Health and Human Services and the Secretary of Agriculture. US Department of Agriculture, Agricultural Research Service, Washington, DC. Available at: https://health.gov/dietaryguidelines/2015-scientific-report/PDFs/Scientific-Report-of-the-2015-Dietary-Guidelines-Advisory-Committee.pdf

[69] A joint effort by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF-AICR 2018). Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. The Third Expert Report. Exposure: Non-alcoholic drinks. Available at https://www.wcrf.org/dietandcancer/

> "The mechanisms linking coffee consumption to a decrease in endometrial cancer risk remain unclear but may involve lower circulating levels of bioavailable sex steroids or insulin and higher insulin sensitivity in people who drink coffee. … Coffee has also been shown to alter adipokines and inflammatory pathways and lead to an increase in adiponectin levels – an adipokine that is down-regulated in obesity and has been linked to endometrial cancer development."[70]

The above two expert reviews were based on systematic searches and reviews of the literature and considered bias and confounding in the course of their evaluations[71,72].

No changes were made to the proposed regulation based on this comment.

Comment 19 (CERT[73]): OEHHA asserts that "IARC's findings . . . , when applied to American Cancer Society statistics for California, show that coffee reduces or probably reduces the risk of human cancers that account for 40 percent of cancer diagnoses in women (liver, endometrium, breast)." By this statement, OEHHA appears to suggest that increased coffee consumption will prevent 40% of cancer among women. OEHHA seems oblivious to the critical distinction between association and causation. IARC did not conclude that coffee consumption probably does not cause human cancer; IARC simply reports that inverse associations have been observed.

Response 19: CERT has misinterpreted OEHHA's statement in the ISOR[74], which is based on IARC's findings of inverse associations of drinking coffee with cancers of the liver and uterine endometrium (i.e., risk is reduced) and studies showing either no association or an inverse association for coffee intake and breast cancer. Cancers of the liver, uterine endometrium, and breast account for 40 percent of cancer diagnoses in women and cancers of the liver account for 4 percent of cancer diagnoses in men. OEHHA is not stating that coffee consumption will eliminate these cancers. Instead, OEHHA observes that coffee consumption is likely to either reduce the risk or not affect risk[75] of these particular types of cancers (liver, endometrium, and breast in women and liver in men).

No changes to the proposed regulation were made based on this comment.

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[70] https://www.wcrf.org/dietandcancer/exposures/non-alcoholic-drinks
[71] DGAC (2015), full citation provided in footnote 68. Part C Methodology, pp. 30-46.
[72] WCRF-AICR (2018), full citation provided in footnote 69. A summary of the Third Expert Report. Chapter 2. Judging the evidence. 'Available at: https://www.wcrf.org/dietandcancer/
[73] CERT 18, pp. 90-91
[74] OEHHA (2018), full citation provided in footnote 2, p. 6.
[75] *Ibid*.

Comment 20 (CERT; Smith[76]): The commenters cited Mendelian randomization, an emerging field in epidemiological research, as the main way to uncover causal relationships between coffee and a wide range of health outcomes, including cancer, and they stated that relationships found in observational studies and meta-analyses that are not consistent with these findings are artefactual. They assert that the conclusions regarding inverse associations for coffee and certain cancers are refuted by Mendelian randomization studies published in the past few years. The commenters provided two studies on cancer and coffee consumption using this method.

With respect to associations of different types of cancer and coffee, CERT[77] states:

> "[B]oth Mendelian randomization studies regarding coffee and cancer published to date reflect no causal relationship between coffee consumption and cancer…[T]he several Mendelian randomization studies regarding coffee and chronic diseases and cancer that have been published since the May 2016 meeting of the IARC Working Group on Coffee are consistent in demonstrating that the inverse associations in the observational epidemiological studies of coffee and chronic diseases and cancer are not causal, but are most likely the result of confounding… [T]he Mendelian randomization studies published since IARC's literature review indicate that the reduction in cancer risk in observational studies is artefactual rather than causal, thereby undermining the essential basis for IARC's conclusion and the basis for its new proposed regulation."

Smith[78] notes:

> "As explained in a recent review, 'Mendelian randomization (MR) uses genetic variants to proxy modifiable exposures to generate more reliable estimates of the causal effects of these exposures on diseases and their outcomes. . . . Analyses using genetic variants as instruments to examine associations with outcomes have a number of advantages: i) effect estimates should be less prone to the confounding that typically distorts conventional observational associations, ii) because germline genetic variants are fixed at conception, they cannot be modified by subsequent factors, thus overcoming possible issues of reverse causation, and iii) measurement error in genetic studies is often low as modern genotyping technologies provide relatively precise measurement of genetic variants, unlike the substantial (and at times differential) exposure measurement error which can accompany observations studies (e.g., due to self-report).' Thus,

[76] CERT 18, pp. 2, 41-52; Smith, pp. 2-4
[77] CERT 18, pp. 51-52
[78] Smith, p. 3

whereas observational studies are inadequate to evaluate causality of dietary factors, Mendelian randomization studies can do so."

"In the last few years, Mendelian randomization studies have been published regarding coffee and Type 2 diabetes, Alzheimer's disease, cardiovascular disease, prostate cancer, and epithelial ovarian cancer. These studies have not reported inverse associations for these diseases and indicate that the inverse associations reported in observational studies regarding coffee are not causal, but are most likely due to confounding and reverse causation."

Response 20: First, there is no conflict between the two Mendelian randomization studies discussed by the commenters and the IARC conclusions. The two Mendelian randomization studies were conducted on coffee and cancers of the prostate (Taylor et al. 2017[79]) and ovary (Ong et al. 2018[80]). Both of these studies became available after the IARC determination in 2016. Below we first discuss the findings from each of these Mendelian randomization studies in the context of the IARC conclusions on prostate and ovarian cancer.

Second, to address the notion that Mendelian randomization studies are indicative of true relationships, a brief description of Mendelian randomization studies is given followed by a discussion of the limitations that can bias Mendelian randomization studies and lead to mischaracterized relationships between exposures and disease outcomes, including cancers.

Prostate Cancer Mendelian Randomization study

Taylor et al. (2017)[81] used two genetic variants (*AHR* and *CYP1A1/2*) associated with the propensity for caffeine intake as proxies for coffee consumption to study prostate cancer risk in a sample of 46,697 men of European ancestry from 25 case-control studies. They investigated the associations of the genetic variants with high grade compared to low grade prostate cancer, and non-localized compared to localized prostate cancer, as well as prostate cancer mortality. The genetic variants were not associated with all prostate cancer compared to controls or having high grade compared to low grade disease. The genetic variants were associated with slightly higher odds of non-localized disease compared to localized disease.

[79] Taylor AE, Martin RM, Geybels MS, Stanford JL, Shui I, Eeles R, Easton D et al. (2017). Investigating the possible causal role of coffee consumption with prostate cancer risk and progression using Mendelian randomization analysis. *Int J Cancer*. 140(2):322-328.
[80] Ong JS, Hwang LD, Cuellar-Partida G, Martin NG, Chenevix-Trench G, Quinn MCJ et al. (2018), Assessment of moderate coffee consumption and risk of epithelial ovarian cancer: a Mendelian randomization study. *Int J Epidemiol*. 47(2):450-459.
[81] Taylor et al. (2017), full citation provided in footnote 79.

> "Although point estimates are very close to the null for most findings, we cannot rule out the possibility that coffee may have small effects on prostate cancer. For example, the meta-analysis of coffee and prostate cancer conducted by Lu and colleagues in 2014 reports an OR [odds ratio] of 0.96 for prostate cancer risk for the highest (at least ⩾4 cups per day) compared to the lowest categories of consumption (generally < 1 cup per day)."

This indicates the potential for small beneficial effects.

It bears re-stating here IARC's conclusion regarding the evidence in humans for drinking coffee and prostate cancer:

> "Studies conducted worldwide consistently indicated no increased risk of prostate cancer associated with coffee drinking, with inverse or null associations observed in all studies."[82]

Thus, the Taylor study is consistent with other observational studies showing null association for cancer of the prostate. As discussed below, care should be taken not to over-interpret the results from Mendelian randomization studies that are purported to accurately represent coffee consumption based on surrogates for propensity for caffeine intake.

Ovarian Cancer Mendelian Randomization Study

Ong et al. (2018)[83] also used two genetic variants (*AHR* and *CYP1A1/2*) associated with caffeine intake to study epithelial ovarian cancer risk in 44,062 women of European ancestry. The genetic variants were not associated with an increased risk of all epithelial ovarian cancer risk (OR = 0.92, 95% CI: 0.79–1.06) or high-grade serous epithelial ovarian cancer risk (OR = 0.90, 95% CI: 0.73–1.10).

In the case of ovarian cancer, IARC stated:

> "The evidence for the relation between coffee consumption and risk of cancer of the ovary is based on some 10 cohort and about 20 case-control studies. Evidence from the majority of the cohort studies, including the largest one and a meta-analysis, suggests no association. The evidence from case–control studies is inconsistent; although the majority of studies suggest a null association, some others show (mostly non-statistically significant) positive associations. Given the

[82] IARC (2018), full citation provided in footnote 3, p. 418.
[83] Ong et al. (2018), full citation provided in footnote 80.

> inconsistency of the results among studies, the Working Group found the evidence to be inconclusive."[84]

The Mendelian randomization study on coffee and ovarian cancer by Ong et al. focused on a specific type of ovarian cancer, epithelial ovarian cancer, and did not find any increased risk of this cancer type with the two genetic variants associated with coffee that were the subject of this study. Thus, the findings of this Mendelian randomization study are not in conflict with the conclusions reached by IARC regarding the evidence from the observational studies.

Background on Mendelian Randomization Studies

Mendelian randomization studies use genetic variants as proxies for measured exposures to strengthen causal inference[85]. The benefit of Mendelian randomization studies is that, in theory, genetic variants should not be associated with confounding factors and will not be affected by the disease outcome, thereby eliminating reverse causality. However, there are important assumptions that must be evaluated in order to understand these analyses. As explained by VanderWeele et al. (2014), "the inappropriate use of instrumental variable techniques when the Mendelian randomization assumptions are violated can lead to biases of enormous magnitude."[86] The three key assumptions are that the genetic variant(s): (1) Is associated with the modifiable exposure of interest, (2) is not associated with confounders of the exposure to outcome association and (3) only influences the outcome through the exposure of interest[87]. The following will address each of these assumptions as they apply to Taylor et al. (2017) and Ong et al. (2018).

Assumption 1: The genetic variants are associated with the modifiable exposure of interest (the relevance assumption)

Taylor et al. (2017) and Ong et al. (2018) each selected genetic variants related to the *AHR*[88] and the *CYP1A1/2*[89] genes. Both genes play a functional role in caffeine metabolism and have been studied as proxies for coffee and caffeine consumption in Mendelian randomization studies. However, research has demonstrated that these two

[84] IARC (2018), full citation provided in footnote 3, p. 419.
[85] Davey Smith G and Hemani G (2014). Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet* 23:R89-98.
[86] VanderWeele TJ, Tchetgen EJT, Cornelis M, and Kraft P (2014). Methodological challenges in Mendelian randomization. *Epidemiology.* 25(3): 427-435.
[87] Davey Smith and Hemani (2014), full citation provided in footnote 85.
[88] Taylor et al. (2017) used the single nucleotide polymorphism (SNP) rs4410790 and Ong et al. (2018) used rs6968865
[89] Both studies used the SNP rs2472297

genes are markers for *caffeine* intake, not exclusively *coffee* intake. Cornelis and Munafo (2018) explains some of the issues of using the combination of these two genes as an instrumental variable for coffee:

> "An instrumental variable (IV) that narrows in on a particular aspect of coffee drinking might also face issues of interpretation. For example, genetically-inferred 'fast' and 'slow' caffeine metabolizers may consume different amounts of the same type of coffee, but their circulating caffeine levels may not be different. However, circulating levels of non-caffeine constituents of coffee will differ. Alternatively, given the same amount and type of coffee consumed, slow caffeine metabolizers will, on average, have higher circulating caffeine levels than fast caffeine metabolizers. Circulating levels of non-caffeine constituents will generally be the same. Because most of the SNPs [single nucleotide polymorphisms] associate with caffeine intake, and not exclusively coffee intake, the genetic instrument for coffee might also reflect exposure to other dietary sources of caffeine, which might confound or mask any causal relationship between coffee and outcome. Although MR [Mendelian randomization] studies are thought to be relatively protected against exposure measurement error, this is less likely to be the case for an MR study of coffee or caffeine. For example, the genetic predisposition to drink coffee, due to an increased caffeine metabolism might also impact preference for regular strong coffee over other coffee types."[90]

Therefore, the use of the *AHR* and the *CYP1A1/2* genes as an instrumental variable is not a perfect measure of coffee consumption, because the results are likely confounded by other caffeine-containing beverages such as soda and tea. Both studies specifically acknowledge this point. Ong et al. (2018) explains,

> "the effect of those SNPs (rs2470893, rs2472297 [in *CYP1A2*]) on coffee and caffeine consumption may not be separable…the same applies for SNPs rs6968865 and rs6968554 in *AHR.*"[91]

Taylor et al. (2017) explains,

> "these genetic instruments are not specific to coffee and associate with consumption of other caffeinated beverages (e.g., tea), and even with decaffeinated coffee."[92]

[90] Cornelis MC and Munafo MR (2018). Mendelian randomization studies of coffee and caffeine consumption. *Nutrients.* 10:1343.
[91] Ong et al. (2018), full citation provided in footnote 80.
[92] Taylor et al. (2017), full citation provided in footnote 79.

This is particularly important in a population where tea consumption is high, such as the United Kingdom (UK). Taylor et al. (2018)[93] evaluated the use of caffeine-related genetic variants as proxies for coffee consumption in Mendelian randomization studies by examining beverage consumption and sociodemographic and lifestyle factors. This study found that

> "[a]ssociations of the genetic risk scores with both coffee and tea support the use of coffee genetic risk scores as instruments for amount of coffee and tea consumed (and probably caffeine consumption in general) rather than as specific markers of coffee consumption."[94]

Additionally, the use of the genetic instrument for coffee does not take into account other influences on coffee consumption, such as cultural practices or religion. For example, Seventh-day Adventists are a religious group with very low prevalence of coffee consumption[95].

Assumption 2: The genetic variants are not associated with confounders of the exposure to outcome association (the independence assumption)

This assumption refers to a confounder that is related to both the genetic variant and the outcome, which is difficult to definitively rule out. Ong et al. (2018) stated,

> "Although we found no evidence supportive of an association between the SNPs used and common risk factors for EOC [epithelial ovarian cancer] (e.g. smoking, oral contraceptive use, parity etc.), it is hard to rule out directly possibilities of residual pleiotropy."[96]

This means that there may be associations between the chosen genetic variants and the risk factors for ovarian cancer that are currently unknown.

Assumption 3: The genetic variants only influence the outcome through the exposure of interest (the exclusion restriction assumption)

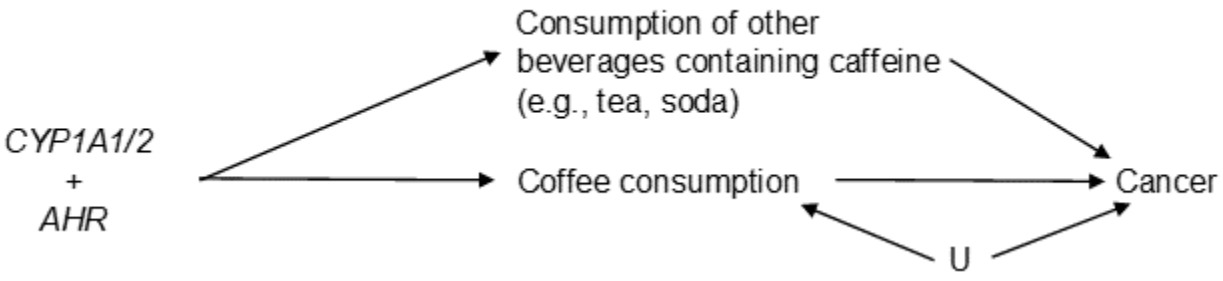
[93] Taylor AE, Davey Smith AE, Munafo MR (2018). Associations of coffee genetic risk scores with consumption of coffee, tea and other beverages in the UK Biobank. *Addiction.* 113:148-57.
[94] *Ibid*.
[95] Phillips RL, Snowdon DA (1985). Dietary relationships with fatal colorectal cancer among Seventh-day Adventists. *J. Natl. Cancer Inst*. 74(2):307-17; Kent LM, Worsley A (2009). Does the prescriptive lifestyle of Seventh-day Adventists provide 'immunity' from the secular effects of changes in BMI? *Public Health Nutr*. 12(4):472-80.
[96] Ong et al. (2018), full citation provided in footnote 80.

There are numerous potential violations of the exclusion restriction that can occur and are not often addressed[97]. An important example of a violation of this assumption is horizontal pleiotropy, or when a genetic variant is associated with multiple exposures or traits that influence the outcome. In both Mendelian randomization studies of coffee and cancer, the possibility of pleiotropy cannot be ruled out, *i.e.,* it has not been established that the genetic variants do not act on cancer risk through pathways unrelated to coffee/caffeine consumption[98].

Another example of a violation is described in VanderWeele et al. (2014). Consider a genetic marker that affects the outcome only through a particular exposure or phenotype, but that this itself consists of two components (X_1, X_2).

> "If only one of these two components, X_1 say, were used in the Mendelian randomization analysis, then there could be substantial bias in the Mendelian randomization estimates of the effect of the exposure on the outcome."[99]

This is illustrated in the following figure, where the genetic variants, *CYP1A1/2* and *AHR*, affect cancer risk through either coffee consumption (X_1) or through other caffeine-containing beverages (X_2), where U represents unmeasured factors.



In this scenario the exclusion restriction is violated because the genetic marker affects the outcome via pathways other than the exposure used in the analysis. Thus,

> "the results of the Mendelian randomization analysis will be biased for the effects of X_1 [coffee consumption] on Y [cancer] and also for the effects of (X_1, X_2) [coffee consumption and other caffeine-containing beverage consumption] on Y."[100]

[97] VanderWeele et al. (2014), full citation provided in footnote 86.
[98] Taylor et al. (2017), full citation provided in footnote 79.
[99] VanderWeele et al. (2014), full citation provided in footnote 86.
[100] VanderWeele et al. (2014), full citation provided in footnote 86.

Taylor et al. (2018) examined associations of coffee genetic risk scores (that included SNPs related to *CYP1A1/2* and *AHR*) with consumption of multiple beverages and

> "found some evidence within UK Biobank for associations with other traits, most notably alcohol consumption. This could be of concern for use of these risk scores as proxies for coffee or caffeine consumption in Mendelian randomization studies, as this would potentially violate the assumption of no horizontal or biological pleiotropy."[101]

Other Mendelian randomization studies using variants in *CYP1A1/2* and *AHR* did not find clear evidence for associations with potential confounders, but they did not investigate alcohol consumption. More work is needed to confirm if this is a true association. However, if it is a true association, it would be a violation of the exclusion restriction assumption, as illustrated above.

Another violation of this assumption would be if either of the genetic variants were in linkage disequilibrium with another genetic marker that affects prostate cancer risk. To entirely avoid such a violation,

> "it would be required that there be nothing on the same chromosome as the genetic marker used in the analysis that also affects the outcome, or that all such variables be controlled. This is a strong assumption and potential violations are numerous."[102]

There were a few other limitations of these two Mendelian randomization studies of coffee and cancer that are important to note. In Taylor et al. (2017), which analyzed data from more than 20 prostate cancer case-control studies, there was heterogeneity between the studies in terms of case definition, treatment received, classification of stage, grade and mortality follow-up. Additionally, the combined SNPs only accounted for a relatively small proportion of variation in coffee consumption in cups per day (~1.2% in Ong et al. 2018). Thus, it does not distinguish between high coffee consumers and low coffee consumers. This can cause problems in power in Mendelian randomization analyses. Finally, the two studies were conducted in European populations and their wider generalizability is unclear.

It is important to understand the limitations of Mendelian randomization studies as they apply in this particular instance of assessing the harmful and beneficial effects of coffee with regards to cancer. Davies *et al.* (2018) note it is also important that the findings

[101] Taylor et al. (2018), full citation provided in footnote 93.
[102] VanderWeele et al. (2014), full citation provided in footnote 86.

> "be interpreted in the context of existing evidence from other sources, using different study designs, and clinical guidelines should not be rewritten solely on the basis of Mendelian randomisation results."[103]

Ong et al. (2018) conclude,

> "[w]e found no evidence indicative of a strong association between EOC [epithelial ovarian cancer] risk and genetically predicted coffee or caffeine levels. However, our estimates were not statistically inconsistent with earlier observational studies, and we were unable to rule out small protective associations."[104]

Ultimately, the two Mendelian randomization studies on surrogate measures of caffeine intake and ovarian and prostate cancers are not in conflict in their conclusions with those on coffee and these cancers drawn by IARC.

No changes were made to the proposed regulation based on this comment.

Confounding

Comment 21 (CERT[105]): The commenter asserted that many of the null or inverse associations "may be influenced by confounding due to factors that have been reported to reduce the risk of" a number of cancers - pancreatic, prostate, breast, colorectal, endometrial, and liver cancer. The commenter lists several factors that are hypothesized to reduce the risk of these cancers and states that the study authors did not adequately control for them.

- Colorectal cancer: dietary factors (Mediterranean diet, cruciferous vegetables, dietary fiber, dairy products, fish, garlic, nuts, omega-3 polyunsaturated fatty acids, and soy and isoflavones), physical activity, vitamins, medications (aspirin, bisphosphonates, and statins), reproductive factors (menopausal hormone therapy and oral contraceptive use)
- Liver cancer: dietary factors (green tea, tea, uncontaminated water, Mediterranean diet and other healthy dietary patterns, dietary fiber, vegetables, fish, ginseng, trace elements and vitamins), medications, hormone replacement therapy and reproductive factors

[103] Davies NM, Holmes MV, Davey Smith G (2018). Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 362:k601.
[104] Ong et al. (2018), full citation provided in footnote 80.
[105] CERT 18, pp. 90-103, 112-119, 133-142, 162-168, 179-206; CERT H1, transcript pp. 26-30

- Endometrial cancer: cigarette smoking, contraceptives, intrauterine devices, aspirin, bisphosphonates, breastfeeding, reproductive factors, physical activity, multiple dietary factors (health dietary patterns, Mediterranean diet, dietary fiber, fruits and vegetables, nuts, soy, and vitamins)
- Breast cancer: physical activity, breastfeeding, multiple dietary factors (calcium, carotenoids, dietary fiber, fatty acids and fish, flavan-3-ols, folate, fruit, Mediterranean diet, soy, vegetables, tea, green tea, and vitamins)
- Pancreatic cancer: physical activity, medications (aspirin, metformin), dietary factors (Mediterranean diet, fruits and vegetables, dietary fiber, whole grains, nuts, unsaturated fatty acids, green tea, plasma adiponectin, vitamins, trace elements), reproductive factors, allergies and asthma, blood group O
- Prostate cancer: medical conditions (Type 2 diabetes, Parkinson's disease, Schizophrenia, and spinal cord injury), medications (aspirin and other NSAIDs, beta-blockers, and metformin), physical activity, dietary factors (Mediterranean diet, fruits and vegetables, lycopene and tomatoes, phytoestrogens, fish and omega-3 fatty acids, soy and soy flavones, tea, wine, certain vitamin precursors (α-carotene and α-tocopherol), selenium, adiponectin), urinary estrogen, reproductive factors, sun exposure.

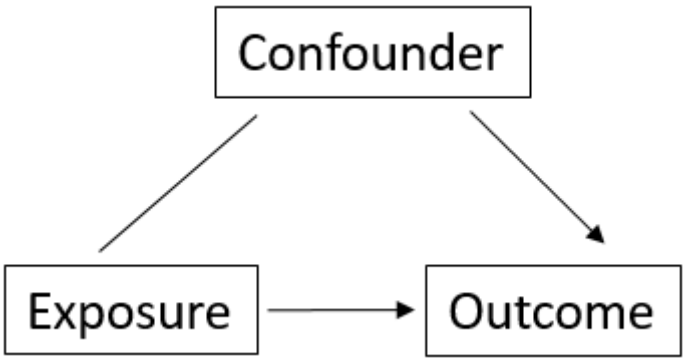
Response 21: The majority of the factors listed above would not be considered as confounders in epidemiologic research on the associations between coffee and the various cancers.

A variable is considered as a confounder when evaluating the relationship between an exposure (e.g., apparent causal factor) and outcome (e.g., cancer) when three requirements are met:

1) the variable can cause or prevent the outcome of interest
2) it is not an intermediate variable in the causal pathway between exposure and the outcome
3) it is associated with the exposure under investigation[106,107].

These are illustrated in this causal diagram, in which the straight line represents a potential association and the arrows represent causal paths:

[106] Rothman KJ, Greenland S, Lash TL (2008). Validity in epidemiologic studies, Chapter 9. In: Rothman KJ, Greenland S, Lash TL editors. *Modern Epidemiology* (3rd Edition). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, pp. 128-147.
[107] Porta, M (ed.) (2014). Dictionary of Epidemiology, Oxford University Press, Incorporated, Oxford. Available from: ProQuest Ebook Central. [Accessed 19 December 2018].



The correct identification of confounders

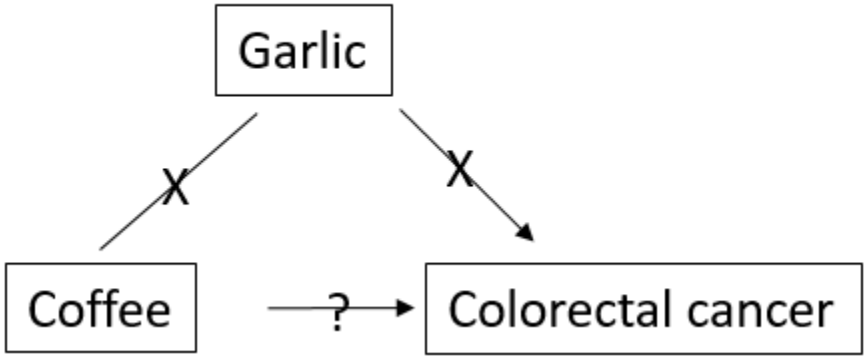
> "requires substantive knowledge about the causal network of which exposure and outcome are part (e.g., pathophysiological and clinical knowledge). Attempts to select confounders solely based on observed statistical associations may lead to bias"[108].

The IARC Preamble provides a clear definition for confounding:

> "Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease."

Many of the factors indicated by the commenter are not confounders because they are not (1) a recognized cause or preventative agent for the specific cancer named by the commenter, and (2) associated with coffee drinking. Thus, it would not be appropriate to treat these factors as confounders. For example, the commenter listed garlic as a potential confounder that has been associated with a reduced risk of colorectal cancer. The association between coffee, colorectal cancer, and garlic can be illustrated in a causal diagram, as shown below:

[108] *Ibid.*



Garlic should not be considered as a confounder because it is not a recognized cause or preventative agent of colorectal cancer, and it is not known to be associated with coffee consumption. This is indicated by the X's, which show that the relationships between garlic and colorectal cancer, and coffee and garlic, are not known relationships that have been scientifically established.

Furthermore, overadjustment can introduce bias (a systematic error) where none was present to begin with. As explained in Chapter 15 (Introduction to Stratified Analysis) of Rothman et al. (2008),

> "Adjustment for variables that violate any of these criteria is sometimes called *overadjustment* and is the analytic parallel of the design error of overmatching…If a variable violates any of these criteria [referring back to the three requirements of a confounding factor described above], its use in conventional stratified analysis…can reduce the efficiency (increase the variance) of the estimation process, without reducing bias. If the variable violates the third criterion, such use can even increase bias"[109].

The assertion that IARC did not consider negative confounders of the association between coffee consumption and these types of cancer is not correct. As discussed in responses to other comments (16, 18, Section III), OEHHA saw no evidence that IARC did not follow its own guidance in its review of coffee. The Preamble of the Monograph clearly shows that, in evaluating human epidemiological studies, reviewers must carefully consider potential confounders. For example,

> "When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in

[109] Greenland S and Rothman KJ (2008). Introduction to stratified analysis, Chapter 15. In: Rothman KJ, Greenland S, Lash TL editors. *Modern Epidemiology* (3rd Edition). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, pp. 258-282.

> the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty"[110].

IARC's attentiveness in considering whether studies adjusted for factors that were determined to be potential confounders is evident throughout the coffee Monograph.

No changes to the proposed regulation were made based on this comment.

Comment 22 (CERT[111]): Coffee epidemiology studies have not accounted for water intake. Inverse associations between coffee intake and cancer may be attributable to increased water intake among coffee drinkers rather than any effect of roasted coffee.

> "In the few studies that have compared coffee consumption and water intake… the risk of cancer associated with higher water intake is lower than the risk of cancer from high coffee consumption. This suggests that reduced risks of cancers observed in coffee epidemiology studies may be due to consumption of water rather than coffee… These studies suggest that coffee does not causally reduce human cancer".

Response 22: In support of the comments that discuss the suggestion that inverse relationships seen with coffee are attributable to water consumption, CERT discussed the results from four papers on bladder cancer[112], two papers on kidney cancer[113] and one paper on colon cancer[114]. For each of these sites, however, contrary to the assertion in the comment, IARC did not conclude there were inverse associations between coffee and cancer. (Regarding the colon, there was "moderate evidence" of an inverse association between coffee and colorectal adenoma, which is a precursor lesion for colorectal cancer.) Rather, IARC concluded there was inadequate evidence of

[110] IARC (2018), full citation provided in footnote 3, p. 20.
[111] CERT 18, pp. 82-83
[112] Slattery ML, West DW, Robison LM (1988). Fluid intake and bladder cancer in Utah. *Int. J. Cancer* 42(1):17-22; Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC et al. (1999). Fluid intake and the risk of bladder cancer in men. *New Engl. J. Med.* 340:1390-1397; Jiang X, Castelao JE, Groshen S, Cortessis VK, Shibata DK, Conti DV et al. (2008). Water intake and bladder cancer risk in Los Angeles County. *Int. J. Cancer* 123:1649-1656; Bai Y, Yuan H, Li J, Tang Y, Pu C, Han P (2014). Relationship between bladder cancer and total fluid intake: a meta-analysis of epidemiological evidence. *World J. Surg. Oncol.* 12:223.
[113] Wolk A, Gridley G, Niwa S, Lindblad P, McCredie M, Mellemgaard A et al. (1996). International Renal Cell Cancer Study. VII. Role of Diet. *Int. J. Cancer* 65:67-73; Hu J, Mao Y, DesMeules M, Dsizmadi I, Friedenreich C, Mery L, The Canadian Cancer Registries Epidemiology Research Group (2009). Total fluid and specific beverage intake and risk of renal cell carcinoma in Canada. *Cancer Epidemiol.* 33:355-362.
[114] Slattery ML, Caan BJ, Anderson KE, Potter JD (1999). Intake of fluids and methylxanthine-containing beverages: association with colon cancer. *Int. J. Cancer* 81:199-204.

carcinogenicity from drinking coffee. Generalizing the small set of findings for tumors in sites where IARC did not discuss inverse relationships to other cancer sites would be speculative and not supported by the overall weight of the evidence.

No changes to the proposed regulation were made based on these comments.

Risk Assessment

Comment 23 (CERT; Bayard; Melnick; CSPI; Coughlin; NCA; CTWG; Sriboonwong[115]): CERT and other commenters stated that coffee contains acrylamide, a Proposition 65 listed carcinogen, and made statements about the potential cancer risks from acrylamide in coffee.

Bayard and CSPI stated that coffee should have a warning because of its acrylamide content, and that epidemiological studies of coffee are not suitable to evaluate the cancer risk of acrylamide in coffee. Some commenters stated that OEHHA should conduct a dose-response analysis for acrylamide in coffee.

On the other hand, one commenter stated, "We conclude that, in spite of acrylamide's known animal carcinogenicity, the human cancer epidemiology database is reassuring and supports the conclusion that there is little if any increased cancer risk in humans." (Coughlin, p. 6[116]). Another commenter stated that, "Because IARC's and OEHHA's determinations relate to the carcinogenicity of *coffee* as a whole, and not to any individual chemical component of coffee, discussions about the carcinogenicity of an individual chemical such as acrylamide are irrelevant to this Rulemaking." (NCA, p. 5)

Response 23: Acrylamide is a genotoxic carcinogen, and coffee contains acrylamide.

OEHHA disagrees that one must view the risk of this particular complex mixture, i.e., coffee, by focusing on a single specific compound such as acrylamide, and ignore the overall scientific evidence on the mixture when considering whether or not the mixture poses a significant risk of cancer[117].

[115] CERT 18, pp. 7-13, 19-37, 223-230; CERT H1, transcript pp. 13-22, 38-42; Bayard, pp. 2, 4-16, 45; Melnick, pp. 5-8, 10-12; CSPI, pp. 3-4; Coughlin, pp. 2-45; NCA, p. 6; CTWG, pp. 1-2; Sriboonwong, p. 1
[116] Coughlin, p. 6 of Appendix F, Coughlin JR and Nehlig A. Coffee and cancer: a benefit-risk evaluation of the experimental and epidemiological evidence. Proceeding of the 24th International Conference of the Association for Science and Information on Coffee (ASIC), San Jose, Costa Rica, November 12.
[117] OEHHA (2018), full citation provided in footnote 2.

This particularly well-studied complex mixture that is coffee contains thousands of chemicals[118,119,120], including carcinogens and chemicals that have cancer chemopreventive properties. Given that it has been studied in animal carcinogenesis bioassays and there is a large literature of human cancer studies, it is appropriate under these particular circumstances to use the evidence on risk for the mixture as a whole (i.e., coffee). This is somewhat analogous to the situation with active and passive tobacco smoking where risks have been addressed by evaluating studies on the mixture rather than inferring the risk of tobacco smoking[121,122] in humans from the results of animal studies for the individual carcinogens in the mixture. However, unlike tobacco smoke, which increases cancers at 15 or more sites, for coffee IARC did not identify increases in cancer at any site, found inverse associations (risk decreases) for cancers of the liver and endometrium, noted possible inverse relationships for breast and colorectal adenoma, a precursor lesion for colon cancer, found inadequate evidence of carcinogenicity in experimental animal studies, and noted inverse associations in several experimental animal studies.

One commenter (Bayard, pp. 5 and 45) submitted a quantitative risk estimate for acrylamide in coffee. He calculated a risk of two cancer cases per 10,000 people for the average coffee drinker based on exposure to acrylamide in coffee. He derived that estimate from animal cancer bioassay data for acrylamide. Here Dr. Bayard's estimate of increased risk for acrylamide in coffee extrapolated from animal data is considered in the context of an estimate of overall risk reduction from human data for cancers showing inverse associations with drinking coffee.

- Liver cancer: IARC concluded that "a consistent, statistically significant, inverse association between coffee drinking and risk of liver cancer has been observed in multiple studies." Further, IARC noted "Compared with no consumption, the summary relative risks for HCC [hepatocellular carcinoma] by random-effect model were 0.66 (95% CI, 0.55–0.78) for regular" coffee drinkers from an

[118] IARC (2018), full citation provided in footnote 3, pp. 64-68.

[119] Jaiswal R, Matei MF, Golon A, Witt M, Kuhnert N (2012). Understanding the fate of chlorogenic acids in coffee roasting using mass spectrometry based targeted and non-targeted analytical strategies. *Food Funct* 3:976-984.

[120] Amanpour A, Selli S (2016). Differentiation of volatile profiles and odor activity values of Turkish coffee and French press coffee. *J Food Process Preserv* 40:1116-1124.

[121] OEHHA (2005). Health Effects of Exposure to Environmental Tobacco Smoke: Final Report. OEHHA, California Environmental Protection Agency, https://oehha.ca.gov/air/report/health-effects-exposure-environmental-tobacco-smoke-final-report; and US Department of Health and Human Services (US DHHS 2014). The health consequences of smoking – 50 years of progress: a report of the Surgeon General. – Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Available at: https://www.ncbi.nlm.nih.gov/books/NBK179276/, pp. 944

[122] Lee PN, Forey BA, Coombs KJ (2012). Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. *BMC Cancer*. 12:385.

updated meta-analysis of prospective studies by Bravi et al. (2017)[123]. Using this estimate of 0.66 for the relative risk of hepatocellular carcinoma in coffee drinkers compared to non-coffee drinkers, and given the overall lifetime risk of liver cancer in the US[124] of 1%, and the prevalence of daily coffee drinking of 74.7%[125], one can calculate the reduction of 46 liver cancers per 10,000 coffee drinkers, with the risk for non-coffee drinkers estimated at 134 per 10,000 and for coffee drinkers at 88 per 10,000 exposed:

- If one assumes 74.7% of the adult population drinks coffee, one can calculate the risk of liver cancer in non-coffee drinking adults as 1.34%[126], or 134 cases in a population of 10,000 non-coffee drinkers.
- Thus the lifetime liver cancer risk for coffee drinkers would be 0.66 × 1.34% = 0.88%
- And the reduction of liver cancer cases would be 134-88 per 10,000, or 46 per 10,000.

- Endometrial cancer: IARC noted, "A meta-analysis published in 2012 found a 30% lower risk of endometrial cancer among coffee drinkers, consistent with the majority of cohort and case–control studies."[127] The lifetime risk of developing endometrial cancer is 2.9% in the US[128]. With this occurrence (using the approach shown for liver cancer) the incidence of endometrial cancers in non-coffee drinkers can be estimated to be 374 per 10,000 and in coffee drinkers it can be estimated to be 261 per 10,000, a difference of 113 per 10,000 persons.

These estimates of risk reduction for the liver and endometrial cancer apply to coffee as a mixture of chemicals – including the acrylamide in the coffee mixture. These hypothetical risk reductions of roughly 160 per 10,000 are considerably larger than the

[123] Bravi F, Tavani A, Bosetti C, Boffetta P, La Vecchia C (2017). Coffee and the risk of hepatocellular carcinoma and chronic liver disease: a systematic review and meta-analysis of prospective studies. *Eur J Cancer Prev*, 26(5):368–77.

[124] According to the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program "approximately 1% of men and women will be diagnosed with liver and intrahepatic bile duct cancer at some point during their lifetime, based on 2013-2015 data." Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer at: https://seer.cancer.gov/statfacts/html/livibd.html

[125] Based on National Cancer Institute estimates from the National Health and Nutrition Examination Survey, reported by Loftfield E, ND Freedman, KW Dodd, E Vogtmann, Q Xiao, R Sinha, BI Graubard (2016). Coffee drinking is widespread in the United States, but usual intake varies by key demographic and lifestyle factors. *J. Nutr.*;146:1762–8.

[126] $Risk_{NC} = Risk_{LIVER}/(F_{NC} + (1-F_{NC})*RR_C)$, where $Risk_{LIVER}$ is the lifetime risk of liver cancer in men and women, R_{NC} is the risk in non-coffee drinkers, F_{NC} the fraction of non-coffee drinkers and RR_C the relative risk of liver cancer in coffee drinkers. Thus $Risk_{NC} = 0.01/(0.253 + 0.747 \times 0.66) = 0.0134 = 1.34\%$

[127] Je Y, Giovannucci E (2012). Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. *Int. J. Cancer*, 131(7):1700–10.

[128] According to the SEER program, "Approximately 2.9 percent of women will be diagnosed with uterine cancer at some point during their lifetime, based on 2013-2015 data." https://seer.cancer.gov/statfacts/html/corp.html

increased risk estimate of Bayard of two per 10,000. They illustrate that, for this particular unique mixture, reliance on a single carcinogenic constituent to infer significant risk can result in a substantial mischaracterization of the risk profile, which appears at least for the liver and uterus to be one of a relatively large risk reduction.

No changes to the proposed regulation were made based on this comment.

Comment 24 (CERT[129]): Epidemiological studies are not suitable to evaluate the risk from acrylamide and other carcinogens in coffee, because the referent group in epidemiology studies are also exposed; multiple adequately powered studies of sufficient duration and follow-up are needed; and epidemiology studies lack the power to detect risks of 10^{-5} or even 10^{-4}. "Null results from epidemiological studies alone do not prove the absence of carcinogenic effects, because of inadequate statistical power, inadequate study design, inadequate follow up, confounding, misclassification of exposure, and other factors." (CERT 18, p. 36)

Response 24: Exposure to acrylamide, one of the carcinogens present in coffee, is ubiquitous, since it is formed during the high-temperature cooking or processing (e.g., frying, roasting, grilling, and baking) of many plant-based foods, including potatoes, grains, and coffee beans. In addition to its presence in certain foods, acrylamide is also present at high concentrations in tobacco smoke.

While it is not possible to study coffee drinking and cancer in a population that is not exposed to acrylamide from sources other than coffee, it is informative to focus on a population that has higher exposures to acrylamide, e.g., smokers. Studies on coffee drinking and cancer that stratify by smoking status allow analysis of the effects of coffee consumption on cancer among smokers, who are more highly exposed to acrylamide[130], and among nonsmokers, who are exposed to lower levels of acrylamide.

Studies have shown that smokers in general have higher levels of certain biomarkers of exposure to acrylamide in their blood than non-smokers. Hemoglobin adducts of acrylamide and its primary metabolite glycidamide, measured in blood, are biomarkers of acrylamide exposure and metabolism[131,132], and reflect exposures to acrylamide that

[129] CERT 18, pp. 33-36
[130] Vesper HW, Bernert JT, Ospina M, Meyers T, Ingham L, Smith A, Myers GL (2007). Assessment of the relationship between biomarkers for smoking and biomarkers for acrylamide exposure in humans. *Cancer Epidemiol Biomarkers Prev* 16(11):2471-2477.
[131] *Ibid.*
[132] Vesper HW, Caudill SP, Osterloh JD, Meyers T, Scott D, Myers GL (2010). Exposure of the U.S. population to acrylamide in the National Health and Nutrition Examination Survey 2003-2004. *Environ Health Perspect* 118:278-283.

have occurred from all sources over the preceding 100-120 days (the lifetime of red blood cells). Biomarker studies have shown that dietary intake and smoking are important determinants of acrylamide and glycidamide hemoglobin adduct levels[133,134,135], and that smokers have greater overall exposure to acrylamide than nonsmokers. Specifically, in a nationally representative sample of the US population, acrylamide adduct levels were 126% higher and glycidamide adduct levels were 101% higher in smokers after adjusting for sociodemographic (age, sex, race-ethnicity, education level, poverty income ratio) and lifestyle (alcohol consumption, BMI, physical activity, dietary supplement use) covariates[136].

Findings from studies of coffee drinking and female breast cancer that stratified by smoking status are discussed below. While the target tumor sites of acrylamide in humans are not known, the mammary gland is a target site of acrylamide in animals, with benign and malignant mammary tumors observed in three studies in female rats[137,138,139] and one study in female mice[140]. Induction of rodent mammary tumors by acrylamide, which is metabolized to the carcinogenic epoxide glycidamide[141], is consistent with the actions of several other epoxide-forming carcinogens, which also induce mammary tumors in rodents[142]. Furthermore, glycidamide itself also induced mammary tumors in one study in female rats and one study in female mice[143].

Also discussed below are findings from studies of coffee drinking and liver cancer that stratified by smoking status. The liver is a target site of acrylamide in animals, with hepatocellular adenoma observed in one study in female rats[144].

[133] Vesper et al. (2007), full citation presented in footnote 130.
[134] Vesper et al. (2010), full citation presented in footnote 132.
[135] Vesper HW, Sternberg MR, Frame T, Pfeiffer CM (2013). Among 10 sociodemographic and lifestyle variables, smoking is strongly associated with biomarkers of acrylamide exposure in a representative sample of the U.S. Population. *J Nutr.* 143(6):995S-1000S.
[136] *Ibid.*
[137] NTP (2012). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Acrylamide (CAS. No. 79-06-1) in F344/N rats and B6C3F1 mice (feed and drinking water studies). NIH Publication No. 12-5917. NTP TR 575, National Institutes of Health, Public Health Service, US Department of Health and Human Services.
[138] Johnson KA, Gorzinski SJ, Bodner KM, Campbell RA, Wolf CH, Friedman MA (1986). Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. *Toxicol Appl Pharmacol* 85(2):154-168.
[139] Friedman MA, Dulak LH, Stedham MA (1995). A lifetime oncogenicity study in rats with acrylamide. *Fundam Appl Toxicol* 27(1):95-105.
[140] NTP (2012), full citation provided in footnote 137.
[141] *Ibid*.
[142] Melnick RL (2002). Carcinogenicity and mechanistic insights on the behavior of epoxides and epoxide-forming chemicals. *Ann. N. Y. Acad. Sci.* 982:177-189.
[143] NTP (2014). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Glycidamide (CAS. No. 5694-00-8) in F344/N Nctr rats and B6C3F1/Nctr mice (drinking water studies). NTP TR 588, National Institutes of Health, Public Health Service, US Department of Health and Human Services.
[144] NTP (2012), full citation provided in footnote 137.

Female breast[145]

IARC has concluded that a positive association has been observed between tobacco smoke and female breast cancer in humans[146]. However, it has not been shown that the risk of breast cancer is higher for smokers who drink coffee than for smokers that do not drink coffee. In fact, in the available studies inverse associations are observed for breast cancer risk in smokers from coffee drinking. These observations indicate that the acrylamide in coffee does not increase the cancer risk.

Two epidemiologic studies of coffee intake and cancer stratified by smoking status were reported in IARC's results: the population-based case-control study of Lowcock et al. (2013)[147] and the prospective cohort study of Gapstur et al. (2017)[148]. Both studies reported inverse or null associations between coffee drinking and breast cancer and reported no difference in these associations when stratified by smoking status. Given that smokers are exposed to higher levels of acrylamide than non-smokers, and that coffee did not increase the risk of breast cancer in smokers, one cannot conclude that exposure to acrylamide present in the complex mixture that is coffee results in an increased risk for breast cancer. The results from these studies for the overall risk from coffee (adjusted for smoking status), the risk from coffee in nonsmokers alone, and the risk from coffee in smokers (ever or former) alone are shown in the table below.

[145] IARC concluded there is *inadequate evidence* for the carcinogenicity of coffee drinking in humans, and there is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancer of the female breast.
[146] International Agency for Research on Cancer (IARC 2012a). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Personal Habits and Indoor Combustion. Tobacco Smoking Volume 100E, World Health Organization, Lyon, France, p. 167. Available at: https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-17/
[147] Lowcock EC, Cotterchio M, Anderson LN, Boucher BA, El-Sohemy A (2013). High coffee intake, but not caffeine, is associated with reduced estrogen receptor negative and postmenopausal breast cancer risk with no effect modification by CYP1A2 genotype. *Nutr Cancer*, 65(3):398–409.
[148] Gapstur SM, Anderson RL, Campbell PT, Jacobs EJ, Hartman TJ, Hildebrand JS, Wang Y, McCullough ML (2017). Associations of Coffee Drinking and Cancer Mortality in the Cancer Prevention Study-II. *Cancer Epidemiol Biomarkers Prev*. 26(10):1477-1486.

Reference; Study details	Exposure Category	Overall risk estimate (95% CI)	Nonsmokers	Smokers	Covariates
			Risk estimate (95% CI)	Risk estimate (95% CI)	
Lowcock et al. 2013; population-based case-control study that studied 3,062 breast cancer cases in Canada	**Regular (caffeinated) coffee**		**Never smoker**	**Ever smoker**	age, ethnicity, physical activity during the teenage years, smoking (for unstratified analyses)
	Never	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	≥5 cups/day	0.71 (0.51-0.98)	0.53 (0.26-1.07)	0.65 (0.44-0.96)	
Gapstur et al. 2017; prospective cohort mortality study that followed 922,896 Cancer Prevention Study-II participants from 1982 through 2012	**Current coffee consumption (cups/day)**		**Never smoker**	**Former smoker**	age, sex, race, marital status, education, alcohol, BMI, physical activity, family history of cancer, red and processed meat/vegetable intake, current tea drinking, smoking (for unstratified analyses)
	Never	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	>0–1	0.93 (0.86–1.01)	0.96 (0.87–1.05)	0.84 (0.70–1.00)	
	2–3	0.90 (0.83–0.97)	0.92 (0.85–1.00)	0.80 (0.68–0.94)	
	4–5	0.87 (0.79–0.95)	0.93 (0.83–1.03)	0.71 (0.59–0.85)	
	6+	0.89 (0.80–0.99)	0.94 (0.82–1.06)	0.74 (0.60–0.92)	

Liver[149]

IARC has concluded that tobacco smoke causes liver cancer in humans[150]. As with breast cancer, there does not appear to be a higher incidence of liver cancer among smokers who drink coffee than smokers who do not drink coffee. In fact, in the available studies, inverse associations are observed for liver cancer risk in smokers from coffee drinking. These observations indicate that the acrylamide in coffee does not increase the cancer risk.

The association between coffee intake and liver cancer stratified by smoking status was reported in several prospective cohort studies (Hu et al. 2008[151]; Inoue et al. 2005[152]; Lai et al. 2013[153]), a pooled analysis of two prospective cohorts (Shimazu et al. 2005[154]), a pooled analysis of two case-control studies (Gallus et al. 2002[155]) and a

[149] IARC concluded there is *inadequate evidence* for the carcinogenicity of coffee drinking in humans, and there is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancer of the liver. IARC also concluded that an inverse association with drinking coffee has been observed with cancer of the liver.
[150] IARC (2012a), full citation provided in footnote 146.
[151] Hu G, Tuomilehto J, Pukkala E, Hakulinen T, Antikainen R, Vartiainen E, et al. (2008). Joint effects of coffee consumption and serum gamma-glutamyltransferase on the risk of liver cancer. *Hepatology*. 48(1):129-136.
[152] Inoue M, Yoshimi I, Sobue T, Tsugane S; JPHC Study Group (2005). Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan. *J Natl Cancer Inst*. 97(4):293-300.
[153] Lai GY, Weinstein SJ, Albanes D, Taylor PR, McGlynn KA, Virtamo J, et al. (2013). The association of coffee intake with liver cancer incidence and chronic liver disease mortality in male smokers. *Br J Cancer*. 109(5):1344-51.
[154] Shimazu T, Tsubono Y, Kuriyama S, Ohmori K, Koizumi Y, Nishino Y, et al. (2005). Coffee consumption and the risk of primary liver cancer: pooled analysis of two prospective studies in Japan. *Int J Cancer*. 116(1):150-154.
[155] Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, et al. (2002). Does coffee protect against hepatocellular carcinoma? *Br J Cancer*. 87(9):956–9.

case-control study (Tanaka et al. 2007[156]). All studies reported inverse or null associations between coffee drinking and liver cancer even when stratified by smoking status. Risks of liver cancer associated with coffee consumption were not elevated in the strata that included smokers (and presumably higher levels of acrylamide). The results from these studies for the overall risk from coffee (adjusted for smoking status), the risk from coffee in nonsmokers (never and/or ex-smokers) alone, and the risk from coffee in current smokers alone are shown in the table below[157].

[156] Tanaka K, Hara M, Sakamoto T, Higaki Y, Mizuta T, Eguchi Y, et al. (2007). Inverse association between coffee drinking and the risk of hepatocellular carcinoma: a case-control study in Japan. *Cancer Sci*. 98(2):214–8.
[157] Lai et al. (2013) did not report stratified results for nonsmokers; stratified results presented here are for individuals that smoke <20 cigarettes per day, and for individuals that smoke >20 cigarettes per day.

Reference; Study details	Exposure Category	Overall Risk estimate (95% CI)	Non smokers Risk estimate (95% CI)	Smokers Risk estimate (95% CI)	Covariates
Hu et al. (2008); prospective cohort study conducted in Finland, with 60,323 participants	**Cups per day Coffee**		**Never and ex-smokers**	**Current smoker**	age, sex, study year, education, diabetes, chronic liver disease, BMI, smoking (for unstratified analyses)
	0–1	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	2–3	0.66 (0.37–1.16)	0.83 (0.42–1.66)	0.22 (0.07–0.68)	
	4–5	0.44 (0.25–0.77)	0.43 (0.21–0.88)	0.31 (0.13–0.78)	
	6–7	0.38 (0.21–0.69)	0.34 (0.16–0.75)	0.32 (0.13–0.79)	
	8+	0.32 (0.16–0.62)	0.27 (0.10–0.78)	0.29 (0.12–0.71)	
Inoue et al. (2005); prospective study in Japan of 90,452 participants	**Coffee intake**		**Never and ex-smokers**	**Current smoker**	sex, age, study area, ethanol intake, green vegetable intake, green tea drinking, smoking (for unstratified analyses)
	Almost never	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	1-2 days/week	0.75 (0.56-1.01)	0.80 (0.54 - 1.18)	0.68 (0.43 - 1.07)	
	3-4 days/week	0.79 (0.55-1.14)	1.07 (0.68 - 1.69)	0.50 (0.27 - 0.93)	
	Total	0.49 (0.36 - 0.66)	0.62 (0.41 - 0.93)	0.4 (0.25 - 0.62)	
	1-2 cups/day	0.52 (0.38 - 0. 73)	0.58 (0.37 - 0.91)	0.47 (0.29 - 0.76)	
	3-4 cups/day	0.48 (0.28 - 0.83)	0.88 (0.44 - I. 78)	0.29 (0.12 - 0.67)	
	5+ cups/day	0.24 (0.08 - 0.77)	0.34(0.05 -243)	0.22 (0.05 - 0.91)	
Lai et al. (2013); prospective cohort study of 27,037 Finnish male smokers	**Cups per day coffee**		**< 20 cigarettes/day**	**> 20 cigarettes/day**	ATBC intervention arm, age, BMI, education, marital status, history of diabetes, alcohol, tea intake, serum cholesterol, smoking (for unstratified analyses) *Note: Also presented were results stratified by <36 and 36+ years smoking showing inverse associations between coffee consumption and liver cancer.*
	Never drinkers	1.35 (0.65–2.82)	0.67 (0.20-2.26)	0.74 (0.33-1.64)	
	0+ – <1	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	1– <2	0.73 (0.48–1.12)	0.43 (0.23- 0.80)	0.45 (0.30-0.68)	
	2- <3	0.52 (0.33–0.82)	0.23 (0.10-0.51)	0.24 (0.15-0.38)	
	3- <4	0.45 (0.26–0.78)	0.17 (0.05-0.59)	0.14 (0.07-0.27)	
	4+	0.53 (0.30–0.95)	0.10 (0.01-0.73)	0.07 (0.03-0.18)	
Shimazu et al. (2005); pooled analysis of two prospective cohort studies in Japan with 47,605 participants	**Coffee intake**		**Never smoker**	**Current smoker**	age, gender, history of liver disease, alcohol consumption, smoking (for unstratified analyses) *Note: Former smokers also showed inverse associations between coffee drinking and liver cancer*
	Never	1.0 (reference)	1.0 (reference)	1.0 (reference)	
	Ocassionally	0.71 (0.46·1.09)	0.90 (0.38-2.11)	0.80 (0.36-1.75)	
	1+ cups/day	0.58 (0.36·0.96)	0.27 (0.06-1.32)	0.90 (0.41-1.97)	
Gallus et al. (2002); pooled analysis of two case-control studies from Greece and Italy that included 834 cases of hepatocellular carcinoma and 1912 controls	**Cups per day coffee**		**Never and ex-smokers**	**Current smoker**	study, age, sex, education, tobacco smoking, alcohol drinking, BMI, and history of diabetes and hepatitis, smoking (for unstratified analyses).
	Non drinkers	1.0 (reference)	≤ 1 (reference category)	≤ 1 (reference category)	
	1	1.2 (0.9 – 1.6)			
	2	1.0 (0.7 – 1.3)	1.0 (0.7 – 1.3)	0.7 (0.5 – 0.9)	
	3+	0.7 (0.5 – 1.0)	0.7 (0.5 – 1.1)	0.6 (0.4 – 1.0)	
Tanaka et al. (2007); case-control study with 209 cases of hepatocellular carcinomas, 1308 community controls, and 275 hospital-based controls	**Daily coffee use during last 1–2 years**		**Never and ex-smokers**	**Current smoker**	sex, age, heavy alcohol use, hepatitis B surface antigen, antibodies to hepatitis C virus, smoking (for unstratified analyses) *Note: Results shown are for analyses with community controls. Inverse or null associations were observed for analyses with hospital controls.*
	None	1.0 (reference)	Non-daily (reference category) vs daily coffee	Non-daily (reference category) vs daily coffee	
	Occasional	0.31 (0.21–0.46)			
	1-2 cups	0.11 (0.06–0.21)	0.23 (0.12–0.42)	0.14 (0.06–0.32)	
	3+ cups	0.10 (0.04–0.24)			

In summary, inverse or null associations between coffee and cancers of the breast and liver were consistently observed in epidemiologic studies. There was no increase in cancer risk from coffee among smokers, who have elevated acrylamide exposures likely to be at least twice as high as would occur only from the diet (based on a biomarker study conducted in a representative sample of the US population[158]). These data do not support a significant carcinogenic effect of acrylamide in the coffee mixture.

No changes to the proposed regulation were made based on this comment.

Comment 25 (CERT; Melnick; Bayard[159]): Coffee is a mixture that contains several other chemicals that are carcinogens and harmful chemicals, including acrylamide and caffeine. California's coffee drinkers will be subjected to increased cancer risks without the notification that Proposition 65 intended. OEHHA should follow US EPA's guidance on assessing health risks of chemical mixtures, namely that "environmental exposures…to a mixture with a known carcinogenic component may pose a cancer risk in spite of negative results from a whole-mixture study"[160].

Response 25: OEHHA has not found that California's coffee drinkers will be subjected to significant increases in cancer risks from drinking coffee, as discussed at length in responses to several comments above (e.g., Responses 15, 16, 23, 24). OEHHA's approach to assessing the potential cancer risk posed by the complex chemical mixture that is coffee, as discussed here and in the ISOR, is consistent with the US Environmental Protection Agency's (US EPA) guidance on assessing health risks of chemical mixtures.

The US EPA guidance states,

> "If whole-mixture data are available, then one approach to the health risk evaluation of a chemical mixture is to perform a risk assessment using health effect, dose response, and exposure data on the complex mixture…For predicting the effects of subchronic or chronic exposure to mixtures, the preferred approach is to use subchronic or chronic health effect, dose-response, or exposure data on the mixture of concern and adopt procedures similar to those used for single compounds, either systemic toxicants or carcinogens"[161].

[158] Vesper et al. (2013), full citation provided in footnote 135.
[159] CERT 18, p. 228; Melnick, p. 6; Bayard, p. 2
[160] US Environmental Protection Agency (US EPA 2000). Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002, Washington, D.C. Available from http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=4486
[161] US EPA (2000), full citation provided in footnote 160, pp. 37-40.

US EPA guidance goes on to explain that, in the absence of health effects data on the mixture of concern, it would be appropriate to take the next approach, which is to conduct a risk assessment on a similar mixture. If such data are not available, only then would it be appropriate to investigate the single components in the mixture of concern. In the case of coffee, where abundant "whole-mixture" data are available from cancer epidemiology and animal toxicology studies, the preferred approach is to use these data in assessing cancer risk.

The commenter takes the following quoted passage from the US EPA guidance document out of context:

> "…Environmental exposures… to a mixture with a known carcinogenic component then may pose a cancer risk in spite of negative results from a whole-mixture study."[162]

The preceding text is found in a section of the US EPA guidance meant to address a specific set of circumstances. The US EPA provides an example, where animal cancer testing of a simple two-chemical mixture (one a chemical carcinogen and one a highly toxic chemical) fails to demonstrate any mixture-related increase in tumors because the highly toxic chemical kills the animals before tumors can develop:

> "… **at doses of the mixture sufficient to induce a carcinogenic effect, the toxicant could induce mortality so that at the maximum tolerated dose of the mixture, no carcinogenic effect could be observed.** Since carcinogenicity is generally considered by the Agency to be an effect of concern even at extremely low doses, it may not be prudent to conclude that the lack of a carcinogenic effect from such a bioassay indicates the absence of cancer risk at lower doses…Consequently, the mixture approach should be modified to allow the risk assessor to evaluate the potential for masking, of one effect by another, on a case-by-case basis." [emphasis added]

It is clear that the type of circumstances the US EPA is referring to in this section of the guidance does not apply to coffee. In the human studies on coffee there was not toxicity that could mask carcinogenic activity. In the long-term studies in experimental animals, there is clearly not a toxic effect that caused early deaths in animals, and overall the studies showed reduced cancer occurrence in coffee-treated groups compared to control animals (See Responses to Comments 15, 26, 51, 56). Thus, OEHHA's approach to evaluating coffee is consistent with US EPA's guidance.

No changes to the proposed regulation were made based on this comment.

[162] US EPA (2000), full citation provided in footnote 160, pp. 39-40; cited by Melnick, p. 6

Anti-Carcinogens in Coffee

Comment 26 (CERT; Bayard; Melnick[163]): OEHHA, in its Initial Statement of Reasons, presents a statement that coffee contains "numerous chemicals with biological activities associated with protective, anti-carcinogenic effects," including antioxidants and free radical scavengers. A single "obscure article published in an obscure journal", Priftis et al. (2015), is cited by OEHHA in support of this assertion. CERT questions whether this article was "properly peer-reviewed by disinterested scientists," and stated that the word "anti-carcinogenic" does not appear in the main text of the article and therefore is not a conclusion of the article. Whether or not this assertion is true, in order to dismiss the carcinogenic risk of acrylamide, which exerts its carcinogenicity through conversion to its active metabolite glycidamide, OEHHA must show that these chemicals could interfere with the glycidamide carcinogenic process *in vivo*, and that there is enough quantity of those chemicals in the coffee mixture to be effective at doing so. For example, there are also antioxidants and free radical scavengers in tobacco smoke. Antioxidants in coffee have little or no impact on the mechanisms of mutagenicity and carcinogenicity of acrylamide.

Response 26: OEHHA disagrees with the comment. OEHHA's statement that coffee contains "numerous chemicals with biological activities associated with protective, anti-carcinogenic effects" is supported by a large body of literature, some of which was cited in the ISOR. In discussing biological activities associated with protective, anti-carcinogenic effects of coffee and its constituents in Section D, "Coffee is a complex mixture of carcinogens and anticarcinogens" of the ISOR, OEHHA cited a number of references, including IARC (2018)[164], Priftis et al. (2015)[165], and several others. Priftis et al. (2015)[166], which assessed the antioxidant activities of green and roasted coffee bean extracts from 13 coffee varieties, is one of many relevant studies in the published literature. For example, IARC (2018)[167] reviewed numerous studies on the effects of coffee on oxidative stress and antioxidant status (four cross-sectional studies in humans, six randomized controlled trials in humans, 13 intervention (including acute intervention) studies in humans, and multiple studies in human cells *in vitro* and in rodents *in vivo*) and concluded

> "There is *strong* evidence that coffee drinking induces antioxidant effects."

[163] CERT 18, pp. 206-207, 235-237; CERT H1, transcript pp. 30, 40; Bayard, p. 4; Melnick, pp. 2-4
[164] IARC (2018), full citation provided in footnote 3.
[165] Priftis A, Stagos D, Konstantinopoulos K, Tsitsimpikou C, Spandidos DA, Tsatsakis AM, Tzatzarakis MN, Kouretas D (2015). Comparison of antioxidant activity between green and roasted coffee beans using molecular methods. *Mol Med Reports*. 12:7293-7302.
[166] *Ibid.*
[167] IARC (2018), full citation provided in footnote 3, pp. 378-385, 422.

In addition, the World Cancer Research Fund and American Institute for Cancer Research in its Continuous Update Project expert panel also stated coffee contains a number of bioactive compounds that may have beneficial effects "ranging from antioxidant, anti-inflammatory properties to the inhibition of angiogenesis", and "coffee has been shown to alter adipokines and inflammatory pathways"[168] (see Responses to Comments 18 and 70). Another observation of IARC of effects of coffee associated with cancer prevention is that "There is evidence that coffee drinking is associated with a beneficial effect on liver fibrosis and cirrhosis", effects associated with increased risk of liver cancer.

OEHHA disagrees that in order to find that coffee consumption poses no significant risk of cancer, it is necessary to 1) show that acrylamide and its metabolite glycidamide may interact with other chemicals present in coffee, 2) show that other chemicals in coffee can interfere with the carcinogenic actions of acrylamide and glycidamide, and 3) that these other chemicals are present in coffee in amounts sufficient to be protective *in vivo*. As discussed above, there is a robust body of evidence in humans on the carcinogenicity of the complex chemical mixture itself and several long-term carcinogenicity studies of coffee in rats and mice and co-carcinogenesis studies in animals. IARC found the studies to be adequate in terms of study design, conduct and reporting and the evidence of carcinogenicity to be inadequate in humans and in animals, with evidence suggesting lack of carcinogenicity for the liver, uterine endometrium, female breast, pancreas, and prostate. Further, IARC found inverse associations (risk decreases) for cancers of the liver and endometrium, and noted possible inverse relationships for breast and colorectal adenoma, a precursor lesion for colon cancer. These findings in humans are consistent with the overall reductions in tumor incidence or multiplicity seen in animal studies of coffee[169].

Thus, OEHHA has determined that it is most appropriate to use the evidence on the mixture to consider the significance of cancer risks for the overall coffee mixture, rather than making a significant risk determination based on the presence of acrylamide alone without regard to the carcinogenicity of the mixture as a whole. This is consistent with the US EPA guidance for health risk assessment of chemical mixtures, which recommends that "risk assessments on chemical mixtures are best conducted using toxicologic data on the mixture of concern"[170] (see also the Response to Comment 25).

No changes to the proposed regulation were made based on this comment.

[168] WCRF-AICR (2018), full citation provide in footnote 69, relevant pages available at: https://www.wcrf.org/dietandcancer/exposures/non-alcoholic-drinks
[169] IARC (2018), full citation provided in footnote 3, pp. 335-353.
[170] US EPA (2000), full citation provided in footnote 160.

Comment 27 (Smith; CERT; NCA[171]): Smith states that "OEHHA suggests that coffee protects against certain cancers by means of an antioxidant mechanism. This is speculative and probably incorrect, because there is no solid scientific evidence that antioxidants in coffee are protective of human health… OEHHA appears to base its conclusion that antioxidants prevent cancer on the IARC Monograph. However, while the Monograph discusses studies of antioxidants in coffee and cancer, those studies show conflicting results and IARC does not conclude that antioxidants in coffee prevent cancer."

CERT states, "OEHHA's claim that antioxidants in coffee prevent cancer is scientifically unsubstantiated and unfounded and lacks relevance to the mechanism of acrylamide-induced cancer."

NCA states that "[T]here is substantial evidence that antioxidants can be 'chemopreventive agents' that have the capacity to 'control cancer incidence.'" They point to several references related to the topic.

Response 27: As explained in the ISOR on page 11, IARC found "there is strong evidence that coffee drinking induces antioxidant effects" in humans, including in randomized controlled trials, and that coffee has been associated with beneficial effects on liver cirrhosis, an important risk factor for liver cancer. IARC cited a number of scientific studies of various designs, including randomized controlled trials, human cell studies *in vitro*, animal studies *in vivo*, and cell-free systems, that found that coffee induces antioxidant effects.

The IARC Monograph summary[172] states the following on coffee's antioxidant effects:

> "There is *strong* evidence that coffee drinking induces antioxidant effects. Largely consistent protective effects were seen in many human studies of various designs, including randomized controlled trials. Some of these studies examined antioxidant status while others demonstrated a general reduction in oxidative stress markers. Similar antioxidant properties of coffee were demonstrated in studies using human intestinal cell lines and lymphocytes. In several studies of short-term exposures in experimental animals, increased antioxidant enzyme activity, glutathione, and sulfhydryls in liver or plasma have been reported. Coffee induces activity of nuclear factor-erythroid-2-related factor (Nrf2). Finally, many different assays in cell-free systems of both coffee and its constituents demonstrated free radical scavenging activity". (Emphasis in original)

[171] Smith, pp. 4-6; CERT 18, pp. 206-221; CERT H1, transcript pp. 25-26, 40; NCA, p. 12
[172] IARC (2018), full citation provided in footnote 3, p. 422.

CERT cites studies that investigated the effects of antioxidant supplements on health outcomes. Many of these studies have found that antioxidant supplements are not associated with a reduced risk of cancer. OEHHA understands that antioxidant supplements may not be beneficial and are not being recommended by organizations like the National Cancer Institute to prevent cancer[173]. However, there is evidence of a difference between the health effects of increased intake of supplements containing high doses of isolated antioxidant compound(s) and increased intake of whole foods and beverages that contain antioxidants[174]. Diets rich in fruits and vegetables, which contain a variety of compounds with antioxidant activity, are recognized as contributing to reduced cancer risk in humans[175,176,177,178]. It is thus appropriate to consider the antioxidant effects of coffee drinking in humans to understand the role of antioxidants in cancer risk in the context of coffee consumption. The human epidemiological studies considered by IARC were conducted specifically with coffee, and the animal and *in vitro* studies considered by IARC[179] were conducted with coffee or coffee extracts.

No changes to the proposed regulation were made based on this comment.

Coffee Compared to Tobacco

Comment 28 (CERT[180]): OEHHA does not mention the important similarity between coffee and tobacco, instead relying on incorrect analogies for political reasons. The most important and relevant analogy between coffee and tobacco is the addictive nature of these chemical mixtures, which rises from the reinforcing properties of caffeine and nicotine.

Response 28: The ISOR discussed tobacco smoke, second hand smoke, diesel engine exhaust, and alcoholic beverages as examples of complex chemical mixtures. Coffee is also a complex chemical mixture. The addictive properties of either caffeine or nicotine are outside the scope of the regulation, which pertains to carcinogenicity.

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[173] National Cancer Institute (2017). Antioxidants and Cancer Prevention. *National Institutes of Health.* Available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet

[174] Bouayed J, Bohn T (2010). Exogenous antioxidants—Double-edged swords in cellular redox state: Health beneficial effects at physiologic doses versus deleterious effects at high doses. *Oxid Med Cell Longev* 3:228-37.

[175] Farvid MS, Chen WY, Michels KB, Cho E, Willett WC, Eliassen AH (2016). Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. *BMJ* 353:i2343.

[176] Maynard M, Gunnell D, Emmett P, Frankel S, Davey S (2003). Fruit, vegetables, and antioxidants in childhood and risk of adult cancer: the Boyd Orr cohort. *J Epidemiol Community Health* 57:218-225.

[177] Riboli E, Norat T (2003). Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr*. 78(3 Suppl):559S-569S.

[178] Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum N, Norat T et al. (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol* 46:1029-56.

[179] IARC (2018), full citation provided in footnote 3.

[180] CERT 18, p. 310; CERT H1, transcript pp. 30-31

No changes to the proposed regulation were made based on this comment.

Comment 29 (CERT[181]): OEHHA's claim that coffee is unique is incorrect. "Epidemiology studies - these are observational studies - of coffee consumption have reported decreased risks of breast cancer, endometrial cancer, melanoma, and thyroid cancer. But this does not make coffee unique among chemical mixtures, because cigarette smoking has also been reported to reduce the risk of these same cancers." Both coffee and tobacco contain cancer chemopreventive compounds, and coffee has been shown to increase the risk of certain cancers. OEHHA's claim that coffee is unique because it has been the subject of very high scientific interest for many years is also incorrect. Tobacco surpasses coffee for scientific interest and studies.

Response 29: The commenter takes OEHHA's statement about coffee's uniqueness out of context. The ISOR states:

> "Coffee is unique in that it shows reductions in certain human cancers, has not been shown to increase any cancers, and is particularly rich in cancer chemopreventive compounds. It is also unusual because it has been the subject of very high scientific interest for many years – IARC reviewed more than 1000 observational and experimental studies investigating the potential carcinogenicity of coffee in humans and animals, and in vitro and other experimental systems."

All of these points, taken together, are what makes coffee a unique complex mixture. The epidemiology evidence on coffee, which includes a number of large, well-conducted prospective cohort studies of drinking coffee, indicates reductions in cancer at certain sites and does not show increased risk of cancer at other sites.

As discussed in the ISOR, other complex chemical mixtures that contain one or more carcinogens, including tobacco smoke[182], environmental tobacco smoke, diesel engine exhaust, and alcoholic beverages, are recognized as cancer hazards. Each of those four complex chemical mixtures has been classified by IARC as "carcinogenic to humans" (Group 1), based on sufficient evidence of carcinogenicity from studies in humans exposed to those chemical mixtures.

With respect to coffee, IARC[183,184] made its findings of inverse associations of cancer risk for individual sites based on the totality of epidemiological evidence for those sites,

[181] CERT 18, pp. 292-310; CERT H1, transcript pp. 28-31
[182] IARC (2012a), full citation provided in footnote 146, pp. 43-211.
[183] IARC (2018), full citation provided in footnote 3, pp. 415-420, 425.
[184] Loomis et al. (2016), full citation provided in footnote 36.

and went beyond the approach reflected in the CERT comment, i.e., a focus on individual findings from individual studies. IARC did not report melanoma and thyroid cancer to be reduced by coffee drinking. However, it did find inverse associations for cancers of the uterine endometrium and liver, and either no association or a modest inverse association for breast cancer, and moderate evidence for the inverse association with colorectal adenoma, a precursor lesion for colorectal cancer. In contrast, for tobacco smoke, IARC found that while there is evidence suggesting lack of carcinogenicity for cancers of the endometrium (post-menopausal) and the thyroid, there is sufficient evidence in humans that tobacco smoke *causes* more than 15 different types of cancers[185].

Coffee seems to be particularly rich in protective, anti-carcinogenic compounds, including antioxidants. As mentioned in the ISOR, coffee itself has been shown to have high levels of antioxidant activity[186], and the beneficial effects of coffee on markers of oxidative stress[187], antioxidant capacity[188,189], and inflammation[190] have been observed in human intervention studies. In contrast, IARC has found that tobacco smoke "contains well established oxidants, co-carcinogens, tumour promoting fractions, and inflammatory agents, as well as cilia-toxic compounds"[191].

OEHHA agrees that both coffee and tobacco smoke have been of very high scientific interest for many years. Scientific interest in coffee has resulted in a rich body of information from adequately designed, conducted and reported studies, including many studies in humans, for which IARC concluded the evidence of carcinogenicity in humans and in animals is inadequate. As noted in the ISOR, IARC's findings on coffee were based on its review of more than 1000 studies in humans, animals, *in vitro* and other experimental systems.

No changes to the proposed regulation were made based on this comment.

[185] IARC (2012a), full citation provided in footnote 146.
[186] Priftis et al. (2015), full citation provided in footnote 165.
[187] Kempf K, Herder C, Erlund I, Kolb H, Martin S, Carstensen M, Koenig W, Sundvall J, Bidel S, Kuha S, Tuomilehto J (2010). Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: a clinical trial. *Am J Clin Nutr* 91:950-957.
[188] Corrêa TA, Monteiro MP, Mendes TM, Oliveira DM, Rogero MM, Benites CI, Vinagre CG, Mioto BM, Tarasoutchi D, Tuda VL, César LA, Torres EA (2012). Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial. *Plant Foods Hum Nutr* 67:277-282.
[189] Agudelo-Ochoa GM, Pulgarín-Zapata IC, Velásquez-Rodriguez CM, Duque-Ramírez M, Naranjo-Cano M, Quintero-Ortiz MM, Lara-Guzmán OJ, Muñoz-Durango K (2016). Coffee consumption increases the antioxidant capacity of plasma and has no effect on the lipid profile or vascular function in healthy adults in a randomized controlled trial. *J Nutr* 146:524-531.
[190] Kempf et al (2010), full citation provided in footnote 187.
[191] IARC (2012a), full citation provided in footnote 146.

Harmful and Beneficial Non-Cancer Effects of Coffee Drinking

Comment 30 (Smith; CERT; CSPI; NCA[192]): Various commenters provided opinions about non-cancer benefits and risks of coffee as a whole, or its constituents. For example,

- Coffee contains caffeine, which is a developmental toxicant.
- Coffee consumption seems generally safe within usual levels of intake, with summary estimates indicating the largest risk reduction for various health outcomes at three to four cups a day, and more likely to benefit health than harm it.

Response 30: This regulation addresses the cancer risk associated with drinking coffee, not other types of risks or health benefits. Such issues are outside the scope of the regulatory proposal.

No changes to the proposed regulation were made based on this comment.

Comment 31 (CSI): Two additional studies published in the Annals of Internal Medicine that tracked the coffee intake of more than 600,000 people over 16 years concluded that coffee drinkers experience lower risk of death from a series of diseases including cancer.

Response 31: OEHHA acknowledges the comment, and notes that neither the studies themselves nor the citations for these studies were provided.

No changes were made to the proposed regulation based on this comment.

Comment 32 (CERT[193]): Sugar, fat and other additives are often added to coffee. **"**Because coffee is naturally bitter, it is typically consumed with sugars, sweeteners, creamers, whiteners, flavorings, and other additives. These additives are not healthy! They contain high levels of sugars and saturated fat, which are known to significantly increase the risk of cardiovascular diseases. Cardiovascular disease is a major risk factor for cancer."

Response 32: OEHHA has determined that exposure to listed carcinogens in coffee that created by and inherent in the processes of roasting or brewing coffee does not pose a significant cancer risk under Proposition 65. This regulation does not address exposures to listed chemicals that are intentionally added to the coffee mixture or enter the mixture as contaminants through a means other than the inherent process of

[192] Smith, pp. 8-9; CERT 18, pp. 238-291; CERT H1, transcript pp. 32-34, 41; CSPI, p. 5; NCA, pp. 15-16
[193] CERT 18, pp. 231-235; CERT H1, transcript pp. 32-33

roasting coffee beans or brewing coffee. Thus, additives such as sugar or creamers are not covered by this regulation.

No changes to the proposed regulation were made based on this comment.

Comment 33 (CERT[194]): "The coffee industry claims that the Scientific Report of the Dietary Guidelines Advisory Committee ("DGAC"), published in 2015, establishes that coffee consumption confers multiple health benefits. ... The claim of multiple health benefits by the coffee industry is both inaccurate and misleading. Most notably, the FDA has never authorized any health claim for coffee."

Response 33: This comment is not relevant to the proposed regulation. However, we note that the FDA Scientific Report of the 2015 Dietary Guidelines Advisory Committee states:

> "… moderate coffee consumption can be incorporated into a healthy dietary pattern, along with other healthful behaviors."
>
> "Strong and consistent evidence shows that consumption of coffee within the moderate range (3 to 5 cups/d or up to 400 mg/d caffeine) is not associated with increased risk of major chronic diseases, such as cardiovascular disease (CVD) and cancer and premature death in healthy adults…In addition, consistent observational evidence indicates that regular consumption of coffee is associated with reduced risk of cancer of the liver and endometrium, and slightly inverse or null associations are observed for other cancer sites"[195].

No changes to the proposed regulation were made based on this comment.

[194] CERT 18, pp. 312-314
[195] DGAC (2015), full citation provided in footnote 68.

Section III: Scientific Issues for Specific Cancer Sites

Some comments were focused on specific cancer sites, with some providing and discussing epidemiology studies of coffee consumption and cancer hazard or risk. Some articles cited or provided were published after the IARC Monograph Volume 116 Working Group met in May 2016. Here we discuss comments on specific cancer sites, organized alphabetically by site. These comments and responses do not necessarily address issues that were already covered above.

Bladder cancer

Comment 34 (CERT; NCA[196]): CERT, in a sub-section (V.D) entitled "Studies reporting increased risk of cancers since the IARC meeting," briefly describes two prospective cohort studies published after the IARC meeting, by Loftfield et al. (2017)[197] and Lukic et al. (2018b)[198], as well as a small prospective study comparing young versus old bladder cancer patients, Singh et al. 2016,[199] and a hospital-based case-control study, Pavanello et al. 2018[200]. CERT states that these studies "all reported increased risks of bladder cancer." NCA reported on the Loftfield et al. and Lukic et al. studies, found in their "surveillance of the literature post-IARC" and note "these studies found that coffee was associated with increased risk, but cautioned that residual confounding may play a role."

[196] CERT 18, pp. 57-59, 84-85; NCA, pp. 19, 23
[197] Loftfield E, Freedman ND, Inoue-Choi M, Graubard BI, Sinha R (2017). A prospective investigation of coffee drinking and bladder cancer incidence in the United States. *Epidemiology* 28(5):685-693.
[198] Lukic M, Nilsson LM, Skeie G, Lindahl B, Braaten T (2018b). Coffee consumption and risk of rare cancers in Scandinavian countries. *Eur. J. Epidemiol.* 33(3):287-302.
[199] Singh JP, Priyadarshi V, Pal DK (2016). A clinicoepidemiological study of young age bladder tumors: An eastern Indian scenario. *J. Cancer Res. Ther* 12:751-754.
[200] Pavanello S, Carta A, Mastrangelo G, Campisi A, Porru S (2018). Relationship between telomere length, genetic traits and environmental/occupational exposures in bladder cancer risk by structural equation modelling. *Int. J. Environ. Res. Public Health* 15:E5.

CERT, in the section entitled "Coffee Consumption Increases the Risks of Several Cancers" (V), briefly describes results from meta-analyses[201,202,203,204,205,206,207,208] of coffee and bladder cancer, in a sub-section (V.B) entitled "Meta-analysis." In doing so, CERT references[209] the 2017 opinion of one of the CERT experts, Peter Infante[210], who summarized those studies.

Response 34: OEHHA has reviewed the observational studies briefly described by CERT and/or NCA released after the IARC 2016 meeting, and determined that they do not contradict the weight of evidence in support of the proposed regulation. The studies, and OEHHA's brief observations, are as follows:

- Loftfield et al. (2017) [211] assessed the role of coffee drinking in bladder cancer in the US-based NIH-AARP Diet and Health Study cohort, initiated in 1995 with a questionnaire and with follow-up ending in 2011. After adjustment for smoking (a cause of bladder cancer) a positive association was observed with coffee consumption, but not once lifelong smoking patterns were taken into account in the model (p=0.16). This large attenuation raises concerns about residual confounding from smoking. There was no evidence of an association in never smokers (HR = 0.87, 95% CI: 0.65–1.17, *p* trend: 0.84). The study authors hypothesize that "residual confounding from imperfect measurement of smoking or unmeasured risk factors may be an explanation for [their] positive findings".

- Lukic et al. (2018b) [212] was a prospective cohort study that used pooled data from the Norwegian Women and Cancer Study and the Northern Sweden Health and Disease Study. This study did not find significant associations between total

[201] Zhou Y, Tian C, Jia C (2012). A dose–response meta-analysis of coffee consumption and bladder cancer. *Prev. Med.* 55(1):14-22.
[202] Bai et al. (2014), full citation provided in footnote 112.
[203] Zeegers MP, Tan FE, Goldbohm RA, van den Brandt PA (2001). Are coffee and tea consumption associated with urinary tract cancer risk? A systematic review and meta-analysis. *Int. J. Epidemiol.* 30(2):353-362
[204] Yu X, Bao Z, Zou J, Dong J (2011). Coffee consumption and risk of cancers: a meta-analysis of cohort studies. *BMC Cancer* 11:96.
[205] Huang TB, Guo ZF, Zhang XL, Zhang XP, Liu H, Geng J, Yao XD, Zheng JH (2014). Coffee consumption and urologic cancer risk: a meta-analysis of cohort studies. *Int. Urol. Nephrol.* 46(8):1481-1489.
[206] Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X et al. (2016). Coffee and cancer risk: A meta-analysis of prospective observational studies. *Sci Rep.* 6:33711.
[207] Wu W, Tong Y, Zhao Q, Yu G, Wei X, Lu Q (2015). Coffee Consumption and bladder cancer: a meta-analysis of observational studies. *Sci Rep* 5:9051
[208] Sala M, Cordier S, Chang-Claude J, Donato F, Escolar-Pujolar A, Fernandez F et al. (2000). Coffee consumption and bladder cancer in nonsmokers: a pooled analysis of case-control studies in European countries. *Cancer Causes Control* 11(10):925-931.
[209] CERT 18, p. 57
[210] CERT 6, Exhibit B, Opinions of Peter Infante, for Phase 2 of the CERT v. Starbucks trial.
[211] Loftfield et al. (2017), full citation provided in footnote 197.
[212] Lukic et al. (2018b), full citation provided in footnote 198.

coffee consumption and risk of bladder cancer for either men or women in moderate or heavy consumer groups, after adjusting for smoking. In subgroup analyses, an increased risk of bladder cancer was found in a mixed group of men and women never smokers who were heavy coffee consumers. While an increased risk of bladder cancer was found in women who were moderate coffee drinkers after adjusting for smoking status, the risk was not increased in women who were heavy coffee drinkers and there was not a dose-related increase in risk with increasing coffee consumption (p-value for trend = 0.56).

- Singh et al. (2016) [213], provided by CERT, is of poor quality in terms of study design, methods and reporting. Specifically, there is no clear referent group and it has additional limitations, rendering it too limited to be considered informative.

- Pavanello et al. (2018) [214], provided by CERT, was a hospital-based case-control study in men published after the IARC meeting that examined the extent to which leukocyte telomere length[215] and bladder cancer risk were modulated by genetic polymorphisms and environmental/occupational exposures using structural equation modeling. Their statistical models analyzed complex relationships between many variables, including lifestyle factors, levels of DNA adducts, and genetic polymorphisms with bladder cancer risk and leukocyte telomere length. The hypothesis of the study was that decreased leukocyte telomere length is associated with increased risk of bladder cancer. However, one of their models found that coffee consumption was associated with increased, rather than decreased leukocyte telomere length, but increased bladder cancer risk. It is difficult to interpret the statistical and mathematical modeling that was used to generate the study findings. Additionally, the controls used in this study were patients with urological non-neoplastic diseases, including hydronephrosis, urolithiasis, malformative urological diseases, prostatic adenoma and hypertrophia, urological traumas, orchiepididymitis, hydrocele and unspecified urinary symptoms[216]. The use of controls with non-neoplastic urological diseases in bladder cancer case-control studies is problematic, since the intake of coffee and other liquids may be affected by the disease, and possibly introduce a bias in the estimates[217]. Hospital-based case-control studies that used controls with

[213] Singh et al. (2016), full citation provided in footnote 199.
[214] Pavanello et al. (2018), full citation provided in footnote 200.
[215] Telomeres are repetitive sequences of DNA present on the ends of chromosomes that protect the structural integrity of the chromosome. Shorter telomere length has been associated with aging and some aging-related diseases.
[216] Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F et al. (2004). GST, NAT, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. *Int. J. Cancer* 110:598–604.
[217] IARC (2018), full citation provided in footnote 3, pp. 135.

diseases that may affect coffee intake were given less weight than other case-control studies in the IARC analyses.

Regarding the meta-analyses provided by CERT:

- Zhou et al. (2012)[218] included 23 case-control studies and five cohort studies. For cohort studies, drinking four cups of coffee/day was not associated with bladder cancer compared to non-drinkers, while case-control studies found a positive association between drinking coffee and bladder cancer. The ultimate conclusion of the authors was:

  "Although data from case-control studies suggested that coffee was a risk factor for bladder cancer, there was no conclusive evidence on this association because of inconsistencies between case-control and cohort studies."

  Two of the 28 studies included in the meta-analysis were not evaluated in IARC (2018). Pavanello et al. (2010)[219] was a hospital-based case-control study, described by the authors as a "case only study" conducted in Italy that found an increased risk of bladder cancer in men who were heavy coffee drinkers. However, this study was limited by small numbers of controls (n=23 for the highest category of consumption). This study was also limited by the use of hospital-based controls with urologic diseases. Studies like this one that are "hospital-based case-control studies that used controls with diseases that may affect coffee intake" were given less weight by IARC than other case-control studies. The other study was a hospital-based case-control study[220] conducted in northern Italy with 341 cases and 491 controls. This study found no association of coffee consumption with bladder cancer.

- Wang et al. (2016)[221], found no association between coffee consumption and bladder cancer. All 10 cohort studies of bladder cancer included in the meta-analysis were reviewed in IARC (2018).

- Bai et al. (2014)[222] was a study focused on the relationship between fluid intake and bladder cancer risk. Although the authors found an increased risk of bladder

[218] Zhou et al. (2012), full citation provided in footnote 201.
[219] Pavanello S, Mastrangelo G, Placidi D, Campagna M, Pulliero A, Carta A, Arici C, Porru S (2010). CYP1A2 polymorphisms, occupational and environmental exposures and risk of bladder cancer. *Eur J Epidemiol*. 25(7):491-500.
[220] D'Avanzo B, La Vecchia C, Negri E, Decarli A, Benichou J (1995). Attributable risks for bladder cancer in northern Italy. *Ann. Epidemiol*. 5:427–431.
[221] Wang et al. (2016), full citation provided in footnote 206.
[222] Bai et al. (2014), full citation provided in footnote 112.

cancer with coffee intake, they suggest the positive findings could be the result of residual confounding by smoking. The criteria for choosing the studies included in the meta-analysis were not clear. Two of the studies included in the meta-analysis were not reviewed in IARC (2018): Wilkens et al. (1996) and Zhang et al. (2010). Wilkens et al. (1996)[223] was a population-based case-control study of 261 cases and 522 controls. The study did not find an association between coffee consumption and bladder cancer risk in men or women. Zhang et al. (2010)[224] was a population-based case-control study of 608 cases and 607 controls in Shanghai, China. The study found no statistically significant associations between coffee drinking (≤160 ml/day or >160 ml/day) and bladder cancer risk. This study adjusted for age, sex, smoking, BMI, history of bladder infection, history of occupation with high risk, and urination frequency. The limitations of this study include the small number of coffee drinkers included in the study (47 out of the 1,215 individuals).

- Zeegers et al. (2001)[225] included hospital- and population-based case-control studies. The paper is poorly reported with respect to bladder cancer risk and coffee consumption. The values reported by CERT are for urinary tract cancers (bladder, urinary tract, and renal pelvis cancers), which were elevated in men and women combined. For bladder cancer, from a plot in the paper (Figure 2), the results were null with relatively wide confidence bounds. It is not clear if studies included in that analysis adjusted for smoking.

- Yu et al. (2011)[226] found coffee consumption was inversely associated with bladder cancer. This study included nine cohort studies, all of which were mentioned in IARC (2018). Two studies that were included in the analyses were excluded by IARC. Snowdon and Phillips (1984) reported on bladder cancer mortality as an end-point, and was excluded by IARC because "the role of coffee in cancer etiology cannot be distinguished from its role in cancer progression or response to treatment." Tripathi et al. (2002) was excluded by IARC "since it was not clear whether smoking was included as a confounder."[227]

[223] Wilkens LR, Kadir MM, Kolonel LN, Nomura AM, Hankin JH (1996). Risk factors for lower urinary tract cancer: the role of total fluid consumption, nitrites and nitrosamines, and selected foods. *Cancer Epidemiol Biomarkers Prev* 5:161–166.
[224] Zhang W, Xiang YB, Fang RR, Cheng JR, Yuan JM, Gao YT (2010). Total fluid intake, urination frequency and risk of bladder cancer: a population-based case–control study in urban Shanghai. *Zhonghua Liu Xing Bing Xue ZaZhi* 31:1120–1124. [Article in Chinese]
[225] Zeegers et al. (2001), full citation provided in footnote 203.
[226] Yu et al. (2011), full citation provided in footnote 204.
[227] IARC (2018), full citation provided in footnote 3, p. 86.

- Huang et al. (2014)[228] found no significant association of coffee consumption with bladder cancer overall. This meta-analysis included five cohort studies, all of which were evaluated by IARC.

The two other meta-analyses cited by CERT were discussed by IARC: Sala et al. (2000)[229], which showed inconsistencies between population-based and hospital-based case-control studies, and Wu et al. (2015)[230], which IARC pointed out did not include a number of cohort studies in their analysis.

In conclusion, taken together, OEHHA does not find that the studies indicate a consistent association between coffee drinking and bladder cancer. The studies discussed in the comments had mixed findings, and some carried substantial limitations such as low statistical power, poor reporting, inadequate control for confounding due to smoking, and selection bias. The additional studies submitted by CERT and NCA thus are not persuasive evidence against IARC's conclusion that "there was no consistent evidence of an association or dose–response relationship between coffee drinking and cancer of the bladder."[231] The additional studies submitted by CERT and NCA also provide no consistent evidence of an association.

No changes to the proposed regulation were made based on this comment.

Brain cancer

Childhood brain cancer

Comment 35 (CERT; NCA[232]): CERT states that "maternal consumption of coffee during pregnancy appears to be associated with an increased risk of childhood brain cancer", discusses the studies considered by IARC, and references one case-control study by Bailey et al. (2017)[233] published after the IARC meeting. NCA also referenced Bailey et al. (2017), stating "No association was found between maternal coffee intake and risk of childhood brain tumors."

[228] Huang et al. (2014), full citation provided in footnote 205.
[229] Sala et al. (2000), full citation provided in footnote 208.
[230] Wu et al. (2015), full citation provided in footnote 207.
[231] IARC (2018), full citation provided in footnote 3, p. 416.
[232] CERT 18, pp. 56-57; NCA, pp. 26-27
[233] Bailey HD, Lacour B, Guerrini-Rousseau L, Bertozzi AI, Leblond P, Faure-Conter C et al. (2017). Parental smoking, maternal alcohol, coffee and tea consumption and the risk of childhood brain tumors: the ESTELLE and ESCALE studies (SFCE, France). *Cancer Causes Control* 28:719-732.

Response 35: Bailey et al. (2017)[234] is a population-based case-control study conducted in France that pooled data from the ESCALE and ESTELLE[235] studies. In the analyses that combined ESTELLE and ESCALE data, no association between maternal coffee drinking during pregnancy and childhood brain tumors was observed comparing regular (at least 1 cup/week) to never/occasional consumption, and there was not an increased trend in risk (e.g., OR per cup increase). In the analysis of ESTELLE data only, regular coffee consumption during the first trimester was associated with a slightly increased risk of childhood brain tumors, but without an indication of a dose-related trend (OR per cup increase = 1.02, 95% CI: 0.98–1.06). This is the only study that has investigated this specific exposure period (the first trimester). Maternal consumption of coffee during pregnancy was not associated with any subtype of childhood brain tumor (ependymoma, astrocytoma, embryonal tumors, or other glioma). The study authors concluded: "No association was seen between CBT [childhood brain tumors] and the mother smoking or drinking alcohol, coffee, or tea during the index pregnancy."[236]

The IARC Monograph discussed three population-based case-control studies on prenatal exposure to coffee and risk of childhood brain tumors, and concluded "the sparse evidence available for [brain cancer (in both adults and children)] did not permit conclusions to be drawn." As IARC pointed out, "the main limitation was suboptimal response rates, leading to the potential for selection bias". With this additional study by Bailey et al. (2017), which concluded that there was not an association between exposure to coffee and childhood brain tumor, the evidence remains sparse.

No changes to the proposed regulation were made based on this comment.

Adult brain cancer

Comment 36 (NCA[237]): NCA discussed one cohort study (Ogawa et al. 2016[238]) and one case-control study (Malmir et al. 2017[239]) that were published after the IARC 2016 meeting and stated "these studies saw an inverse association between coffee

[234] Bailey et al. (2017), full citation provided in footnote 233.
[235] ESCALE and ESTELLE are population-based case–control studies of childhood malignancies conducted nation-wide in France. ESCALE only included malignant brain tumors, while the ESTELLE study included malignant and non-malignant tumor cases.
[236] Bailey et al. (2017), full citation provided in footnote 233.
[237] NCA, p. 27
[238] Ogawa T, Sawada N, Iwasaki M, Budhathoki S, Hidaka A, Yamaji T et al. (2016). Coffee and green tea consumption in relation to brain tumor risk in a Japanese population. *Int J Cancer* 139:2714-21.
[239] Malmir H, Shayanfar M, Mohammad-Shirazi M, Tabibi H, Sharifi G, Esmaillzadeh A (2017). Tea and coffee consumption in relation to glioma: a case-control study. *Eur J Nutr.* doi:10.1007/s00394-017-1575-z.

consumption and risk of glioma" (e.g., higher coffee consumption was associated with lower cancer risk).

Response 36: Ogawa et al. (2016)[240] evaluated a cohort of 106,324 subjects in the Japan Public Health Center-Based Prospective Study who were followed for an average of 18 years. The study found an inverse association of coffee consumption with brain tumor risk in total subjects (HR = 0.47, 95% CI: 0.22–0.98) and in women (HR = 0.24, 95% CI: 0.06–0.99). There was no association between coffee consumption and brain tumor risk in men, and no association by subtype (glioma or meningioma) in men or women.

The other study referenced by NCA, Malmir et al. (2017)[241], was a hospital-based case-control study of Iranian adults with 128 cases and 256 controls. Coffee consumption was associated with a decreased risk of glioma after adjusting for multiple confounders (OR = 0.09, 95% CI: 0.03–0.24).

IARC (2018) stated "the sparse evidence available for [brain cancer (in both adults and children)] did not permit conclusions to be drawn."[242] These studies, when combined with the relatively sparse data sets reviewed by IARC, do not provide enough evidence to draw further conclusions.

No changes to the proposed regulation were made based on this comment.

Breast (Female)

Comment 37 (CERT; NCA[243]): NCA referenced eight studies on breast cancer and coffee published after the IARC review,

- five observational studies - Pervaiz et al. (2017)[244], Arthur et al. (2018)[245], Gapstur et al. (2017)[246], Yaghjyan et al. (2018) [247], Harris et al. (2017)[248]

[240] Ogawa et al. (2016), full citation provided in footnote 238.
[241] Malmir et al. (2017), full citation provided in footnote 239.
[242] IARC (2018), full citation provided in footnote 3, p. 420.
[243] CERT 18, pp. 84-86, 124-129; NCA, pp. 27-30
[244] Pervaiz R, Tosun O, Besim H, Serakinci N (2017). Dietary factors modify post-menopausal breast cancer risk: a case-control study from Turkish Cypriot population. *Biomed Res Ther* 4:1171-84.
[245] Arthur R, Kirsh VA, and Rohan TE (2018). Associations of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women. *Cancer Epidemiol*. 56:75-82.
[246] Gapstur et al. (2017), full citation provided in footnote 148.
[247] Yaghjyan L, Rich S, Mao L, Mai V, Egan KM (2018). Interactions of coffee consumption and postmenopausal hormone use in relation to breast cancer risk in UK Biobank. *Cancer Causes Control* 29:519-525.
[248] Harris HR, Willett WC, Vaidya RL, Michels KB (2017). An adolescent and early adulthood dietary pattern associated with inflammation and the incidence of breast cancer. *Cancer Res* 77:1179-87.

- two meta-analyses – Lafranconi et al. (2018)[249], Bamia et al. (2017)[250]
- one review – Grosso et al. (2017)[251], that stated coffee was associated with a probable decreased risk of breast cancer

In a section on multisite findings NCA included the cohort study of Loftfield et al. (2018)[252], which also reports on breast cancer and coffee association.

NCA stated:

> "Overall, the weight of the evidence suggests no association between coffee intake and breast cancer."

In the CERT section "Studies Reporting Increased Risks of Cancer Since the IARC Meeting" (V.D.2), CERT briefly describes Arthur et al. (2018), Yaghjyan et al. (2018), and Trieu et al. (2017)[253] and reports:

> "Three recent studies found increased risks of breast cancer in relation to coffee consumption."

CERT, under the heading "Inconsistency of Studies" in section VIII.C.1 states that some studies "have reported increases in breast cancer in association with consumption of coffee", and briefly describes study results of 15 studies.

Response 37: Responses to the comments by CERT and NCA are placed in the context of the IARC review and organized by study type.

Case-control studies of coffee and breast cancer

IARC reported on 22 case-control studies, 20 of which were null or provided statistically significant evidence of coffee-related decreases in breast cancer risk. Two tabulated by IARC showed increased breast cancer risk with coffee consumption (Tavani et al.

[249] Lafranconi A, Micek A, De Paoli P, Bimonte S, Rossi P, Quagliariello V et al. (2018). Coffee intake decreases risk of postmenopausal breast cancer: A dose-response meta-analysis on prospective cohort studies. *Nutrients* 10:(2). pii: E112.
[250] Bamia C, Turati F, Guercio V, Guha N, Loomis D, Tavani A (2017). Coffee intake and risk of breast and ovarian cancer: Updated systematic review and meta-analysis. *Ann Nutr Met* 71 Supplement 2:950-51. (conference abstract)
[251] Grosso G, Godos J, Galvano F, Giovannucci EL (2017). Coffee, caffeine, and health outcomes: An umbrella review, Annu Rev Nutr. 37:131-156.
[252] Loftfield E, Cornelis MC, Caporaso N, Yu K, Sinha R, Freedman N (2018). Association of coffee drinking with mortality by genetic variation in caffeine metabolism: findings from the UK Biobank. JAMA Intern Med 178:1086-97.
[253] Trieu PD, Mello-Thoms C, Peat JK, Do TD, Brennan PC (2017). Inconsistencies of breast cancer risk factors between the northern and southern regions of Vietnam. *Asian Pac. J. Cancer Prev.* 18(10):2747-2754.

1998[254]; Bissonauth et al. 2009[255]), but for one of these studies (Bissonauth et al. 2009) no significant increase in risk was apparent when premenopausal and postmenopausal women were analyzed separately. For Tavani et al. 1998, IARC noted "Odds ratios for coffee intake in relation to breast cancer risk, adjusted for several factors including family history of breast cancer, showed no overall association". Seven studies tabulated by IARC showed significant decreases in risk by trend or for at least one coffee-exposed group. IARC noted the main limitation of case-control studies is recall bias and also discussed limitations and strengths of the studies it included, study-by-study.

CERT discussed two case-control studies reviewed in the IARC Monograph – Bissonauth et al. (2009)[256] and McLaughlin et al. (1992)[257] – and two studies published since the IARC Monograph 116 was released – Trieu et al. (2017)[258] and Yaghjyan et al. (2018)[259]. NCA referred to an additional recent case-control study by Pervaiz et al. (2017)[260], and also the Yaghjyan et al. (2018) study discussed by CERT. While NCA and CERT referred to the Yaghjyan et al. study as a case-control study, it is actually a prospective cohort study, and is discussed below with the other prospective cohort studies.

- Bissonauth et al. (2009)[261] was a case-control study of the association between coffee and other dietary factors and risk of breast cancer for non-carriers of *BRCA1⁄2* mutations among French-Canadian women. Cases were 280 early-onset breast cancer patients. Both IARC (p. 240) and CERT note that Bissonauth et al. reported positive associations with breast cancer with higher levels of coffee drinking. However, what CERT fails to report but IARC points out is that when the analysis was repeated by menopausal status the associations were effectively null. For both pre- and post- menopausal women, neither the low nor high coffee consumption groups had significant associations (e.g., Bissonauth et al., Table 4, multivariable adjusted odds ratios and confidence bounds by menopausal status).

- The McLaughlin et al. (1992)[262] study was a study of methylxanthine consumption in 3234 women in New York State. CERT noted that this study

[254] Tavani A, Pregnolato A, La Vecchia C, Favero A, Franceschi S (1998). Coffee consumption and the risk of breast cancer. *Eur. J. Cancer Prev.* 7(1):77–82, as reported in IARC (2018).
[255] Bissonauth V, Shatenstein B, Fafard E, Maugard C, Robidoux A, Narod S et al. (2009). Risk of breast cancer among French-Canadian women, noncarriers of more frequent BRCA1/2 mutations and consumption of total energy, coffee, and alcohol. *Breast J*, 15(Suppl 1):S63–71.
[256] *Ibid.*
[257] McLaughlin CC, Mahoney MC, Nasca PC, Metzger BB, Baptiste MS, Field NA (1992). Breast cancer and methylxanthine consumption. *Cancer Causes Control*, 3(2):175–8.
[258] Trieu et al. (2017), full citation provided in footnote 253.
[259] Yaghjyan et al. (2018), full citation provided in footnote 247.
[260] Pervaiz et al. (2017), full citation provided in footnote 244.
[261] Bissonauth et al. (2009), full citation provided in footnote 255.
[262] McLaughlin et al. (1992), full citation provided in footnote 257.

found increased odds ratio for decaffeinated but not caffeinated coffee, but failed to note the important finding by McLaughlin et al. that "Upon closer examination, no consistent relationship was observed for levels of cup-years of use of decaffeinated coffee, the age at which women first started or stopped drinking decaffeinated coffee and the number of years between first exposure to these beverages and diagnosis (data not shown)" and that "As with most other studies of breast cancer risk and methylxanthines [present in coffee and cocoa], no increased risk was observed for the consumption of coffee or caffeine."

- Pervaiz et al. (2017)[263], referenced by NCA, was a hospital-based case-control study conducted in postmenopausal women of a Turkish Cypriot population. The study had 401 cases and 385 controls; coffee consumption was not associated with breast cancer risk.

- Trieu et al. (2017)[264], provided by CERT, was a hospital-based case-control study that compared risk factors between the northern and southern regions of Vietnam by analyzing each group separately. 127 cases and 269 controls were from the north and 141 cases and 250 controls were from the south. No associations were observed between coffee consumption and breast cancer in women in the northern region, with 2.4% of breast cancer cases being consumers of coffee compared to 5.2% of the controls. In the southern region, drinking at least one cup of coffee per day was associated with an increased risk of breast cancer in post-menopausal women (OR = 2.1, 95% CI: 1.0–4.6) in multivariable adjusted models, but not in pre-menopausal women. Coffee consumption in both controls and cases was greater in the southern region, with the authors noting that "developing urbanization and modernization in the south has led local women to adopt more westernized lifestyles". Along with this increased westernization has come substantially increased breast cancer rates[265]. It is unclear the extent to which coffee consumption is indicative of westernization and changed lifestyles which could confound observed relationships. The article does not specify which factors were controlled for in the analyses of coffee drinking and breast cancer risk, further limiting the informativeness of the study.

[263] Pervaiz et al. (2017), full citation provided in footnote 244.
[264] Trieu et al. (2017), full citation provided in footnote 253.
[265] Jenkins C, Minh LN, Anh TT, Ngan TT, Tuan NT, Giang KB et al. (2018). Breast cancer services in Vietnam: a scoping review. *Glob Health Action* 11(1):1435344, pp. 1-11, doi: 10.1080/16549716.2018.1435344

Prospective cohort studies of breast cancer:

IARC tabulated the results of 22 cohort studies[266], showing the risk estimates of breast cancer and confidence intervals for the different coffee intake levels in the studies. Any given study typically had estimates for multiple levels of coffee intake. The values tabulated were adjusted for covariates (e.g., reproductive factors like hormone replacement therapy use). All but one of the numerous findings tabulated by IARC were null or showed decreased risk with increasing coffee consumption. The one exception was in the study of Bhoo Pathy et al. (2015)[267] there was a significant increase among "moderately low" coffee drinkers that had pre-menopausal breast cancer. However this was not seen for any other coffee intake group ("low", "moderately high", "high"). The trend with increasing coffee intake for the pre-menopausal breast cancer group was not significant. There were null findings for all post-menopausal groups in this study and the trend was not significant, although there was indication of a slightly protective effect (p=0.055). IARC also reported in the narrative descriptions of these studies some sub-analysis of groups, and these findings were also described by CERT. These studies IARC tabulated that are also discussed by CERT are as follows:

- Ishitani et al. (2008)[268]: This study did not find an association with coffee and breast cancer at any intake level or a significant trend with coffee intake. However, Ishitani et al. (2008) reported for women with benign breast disease "a borderline positive association" for coffee and breast cancer. This was also noted by IARC and CERT. Ishitani et al. (2008) also noted increased risk for ER-/PR- breast cancer and tumors larger than two centimeters with coffee consumption. IARC noted the limitations of the study "included the lack of repeated measures of coffee intake, and selective inclusion of participants fulfilling the eligibility criteria for the randomized study."
- Nilsson et al. (2010)[269]: In this study, "total and filtered coffee were not associated with breast cancer risk overall, but there was evidence for effect modification with age/menopausal status" (IARC, p. 220), with an indication in the highest consumption group of increased risk in younger women and decreased risk in older women.

[266] IARC excluded one cohort study due to small number of cancer cases and a lack of adjustment for reproductive factors or smoking.
[267] Bhoo Pathy N, Peeters PH, Uiterwaal CS, Bueno-de-Mesquita HB, Bulgiba AM, Bech BH, et al. (2015). Coffee and tea consumption and risk of pre- and postmenopausal breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Breast Cancer Res*, 17(15):15–0521.
[268] Ishitani K, Lin J, Manson JE, Buring JE, Zhang SM (2008). Caffeine consumption and the risk of breast cancer in a large prospective cohort of women. *Arch. Intern. Med.* 168(18):2022–31.
[269] Nilsson LM, Johansson I, Lenner P, Lindahl B, Van Guelpen B (2010). Consumption of filtered and boiled coffee and the risk of incident cancer: a prospective cohort study. *Cancer Causes Control* 21(10):1533–44.

- Bhoo Pathy et al. (2010)[270]: CERT reports on a finding in the study that was not significant after adjustment for covariates. The covariate analysis is the more appropriate basis for judging study outcome.
- Vatten et al. (1990)[271]: CERT reports on a non-significant association of coffee consumption and breast cancer in obese women in the study and the significant finding of decreased risk with coffee consumption among lean women. While for this early study IARC notes as its strengths "comprehensive definition of cases, validation of questionnaire for coffee intake" it also notes major limitations: "small number of cases, possibility of information bias, no information/adjustment for important risk factors (e.g. reproductive or smoking), assessment of coffee at baseline only".

In addition to these cohort studies, CERT refers to the study of Lehrer et al. (2013)[272] that considers the effect of coffee on breast cancer survivorship, and the findings from Zhu et al. (2013)[273], which was a meeting abstract only. There is not sufficient detail in a meeting abstract to appraise the strengths and weaknesses of the study and to examine in detail its findings. We also note that as a meeting abstract the study would not meet the IARC requirement for full consideration and summarization[274]. Lehrer et al. (2013)[275] examined the association between coffee intake and breast cancer mortality over 20 years of follow-up in 96 women treated for invasive breast cancer and found coffee had a significant effect on survival. The authors concluded:

> "One possible interpretation of our results suggests that there is an abnormal hypothalamic–pituitary–adrenal axis functioning in breast cancer patients with persistent fatigue, who might be using coffee to self-medicate. In other words, coffee consumption in the present study might be a surrogate marker for fatigue. Because of the paucity of data regarding caffeine intake, poor sleep, fatigue, and breast cancer survival, further studies could be worthwhile."[276]

An additional case-cohort study, Arthur et al. (2018), was discussed by CERT in the section on studies reporting an increased risk since the IARC meeting, and by NCA. In

[270] Bhoo Pathy N, Peeters PH, van Gils C, Beulens JW, van der Graaf, Bueno-de-Mesquita HB, et al. (2010). Coffee and tea intake and risk of breast cancer. *Breast Cancer Res Treat*, 121(2):461-7.
[271] Vatten LJ, Solvoll K, Løken EB (1990). Coffee consumption and the risk of breast cancer. A prospective study of 14,593 Norwegian women. *Br. J. Cancer* 62(2):267–70.
[272] Lehrer S, Green S, Rosenzweig KE (2013). Coffee consumption associated with increased mortality of women with breast cancer. *J. Caffeine Res.* 3(1):38-40.
[273] Zhu L, Butler L, Wang R, Koh WP, Yu MC, Yuan JM (2013). Coffee consumption increases risk of advanced breast cancer among Singapore Chinese women.
[274] IARC (2018), full citation provided in footnote 3, p. 12.
[275] Lehrer et al. (2013), full citation provided in footnote 272.
[276] Lehrer et al. (2013), full citation provided in footnote 272.

addition there is the Yaghjyan et al. (2018)[277] study discussed in the CERT section on case-control studies, and noted by NCA as such, that is a prospective study. NCA briefly describes two additional cohort studies by Gapstur et al. (2017)[278] (also cited by CERT in comments on other sites) and Harris et al. (2017)[279]. These more recent cohort studies are discussed below.

- Yaghjyan et al. (2018)[280], discussed by NCA and CERT, was a study from the UK Biobank cohort that investigated the association of coffee consumption with postmenopausal breast cancer risk. Overall, coffee consumption was not associated with breast cancer risk. (Hazard Ratio (HR) 1.04, 95% CI 0.93–1.16 for 1 cup/day, HR 1.00, 95% CI 0.91–1.11 for 2–3 cups/day, and HR 0.98, 95% CI 0.87–1.10 for at least four cups/day). However, the authors found a positive association of coffee intake with breast cancer in women with a history of postmenopausal hormone therapy who consumed at least four cups of coffee per day compared to women consuming less than seven cups per week (HR = 1.22, 95% CI: 1.01–1.47). On the other hand, no association was found with current hormone use. Also, women with no history of postmenopausal hormone therapy who consumed at least four cups of coffee per day had a reduced risk compared to women consuming less than seven cups per week (HR = 0.84, 95% CI: 0.71–1.00). Strengths of the study were that it adequately controlled for confounders and did sensitivity analyses to exclude participants who developed breast cancer within two years from the date of enrollment. The authors concluded:

  > "While we did not observe any associations in the overall analysis, our findings suggest that coffee consumption might be associated with an increased breast cancer risk in women who used postmenopausal hormones in the past. However, in the absence of any association among current PMH users, these findings are inconsistent with our hypothesis and likely represent a chance finding."[281]

- Arthur et al. (2018)[282], discussed by CERT and NCA, is a prospective study of 3,185 Canadian women that investigated the association between coffee intake and risks of breast, endometrial, and ovarian cancers, with a median 12.2-year follow-up. The study employed a case-cohort design: "A subcohort comprising 3185 women was created by randomly selecting an age-stratified sample of participants from the total cohort at baseline (N=39,618 females)." There was no

[277] Yaghjyan et al. (2018), full citation provided in footnote 247.
[278] Gapstur et al. (2017), full citation provided in footnote 148.
[279] Harris et al. (2017), full citation provided in footnote 248.
[280] Yaghjyan et al. (2018), full citation provided in footnote 247.
[281] Yaghjyan et al. (2018), full citation provided in footnote 247.
[282] Arthur et al. (2018), full citation provided in footnote 245.

association between coffee intake for any level of exposure and the risk of breast cancer overall, and there was not a significant trend with increasing exposure. There was a similar lack of significant associations when coffee was segregated into caffeinated and decaffeinated groups. Further segregation of groups by pre-menopausal, post-menopausal and hormone replacement therapy use found no significant associations for different exposure groups for coffee (caffeinated and decaffeinated), caffeinated coffee, or decaffeinated coffee with one exception. There was an increased hazard ratio (HR) in premenopausal women drinking 3-4 cups of caffeinated coffee, but not in premenopausal women drinking four or more cups a day. There were no significant findings where a continuous model was used to examine per cup increases in coffee, caffeinated coffee, decaffeinated coffee or for each of these by menopausal or hormone replacement status. Similarly there were no significant findings where a continuous model was used to examine per cup increases in coffee, by BMI, for coffee, caffeinated coffee, or decaffeinated coffee. There was a significant finding for BMI>25 and drinking 3-4 cups of caffeinated coffee, but not for four cups or more a day. There was a weak dose related trend just significant (p=0.05) based on strata for coffee intake among the normal weight group (BMI ≤ 25) that was not statistically significant in the continuous per cup increase analysis for the same BMI group. The authors noted that the weak positive associations reported "are possibly due to chance". The authors called for further studies to clarify the role coffee may play in breast, ovarian and endometrial cancers.

- Loftfield et al. (2018)[283], referenced by NCA in the section of its comments on multiple cancer sites, was a prospective cohort study that evaluated associations of coffee drinking with all-cause and cause-specific mortality in the UK Biobank. Coffee consumption was not associated with increased risk of death from breast cancer in multivariable-adjusted models.

- Gapstur et al. (2017)[284], the large prospective cohort study that was discussed by NCA and CERT and cited in CERT's discussion of total cancer mortality, followed 922,896 Cancer Prevention Study-II participants from 1982 through 2012. Among non-smokers, coffee consumption was inversely associated with female breast cancer (HR: 0.97; 95%CI: 0.94–0.99). The study authors stated: "We observed an inverse relationship between coffee consumption and breast cancer mortality (i.e., risk decreased by 3% per two cups/day increase)…"

[283] Loftfield et al. (2018), full citation provided in footnote 252.
[284] Gapstur et al. (2017), full citation provided in footnote 148.

- Harris et al. (2017)[285], cited by NCA, studied pre- and post- menopausal breast cancer with "whether an adolescent and early adulthood inflammatory dietary pattern was associated with breast cancer" (pre- and post- menopausal). Coffee was placed in the "inflammatory dietary pattern" along with "high intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat, and margarine, and low intake of green leafy vegetables, cruciferous vegetables." There was not a separate and independent reporting on coffee alone, and thus this study while interesting is non-informative for considering the separate impact of coffee on breast cancer risk.

Meta-analyses of coffee and breast cancer

IARC cited three meta-analyses that were also cited by CERT: Tang et al. 2009; Yu et al. 2011; Li et al 2013. These reported null or decreased risk of breast cancer with coffee consumption. IARC focused on the large meta-analysis of Jiang et al. (2013), discussed further below. This and the remaining meta-analyses raised by CERT or NCA or both are:

- Jiang et al. (2013)[286]: IARC focused on this large relatively recent study and noted "The overall meta-relative risk of breast cancer (fixed-effects model) was 0.97 (95% CI: 0.93–1.00) for the highest compared with lowest coffee consumption, whereas the meta-relative risk for an increment of 2 cups/day was 0.98 (95% CI: 0.96–1.00)... No significant association was found between risk of breast cancer and consumption of decaffeinated coffee." Thus, the overall finding was a small risk decrement.
- CERT reported on a meta-analysis by Wang et al. (2016)[287]. This study included 17 cohort studies, all of which were evaluated in IARC (2018), and found no statistically significant relationships between coffee consumption and the risk of breast cancer overall and in all subgroups.
- Lafranconi et al. (2018)[288]: This meta-analysis referenced by NCA included 21 prospective studies and found no association between coffee consumption and breast cancer risk overall, and an inverse relationship in postmenopausal women. All studies included in the analysis were evaluated in IARC (2018) except Harris et al. (2015)[289]. This study was a prospective cohort study of

[285] Harris et al. (2017), full citation provided in footnote 248.
[286] Jiang W, Wu Y, Jiang X (2013). Coffee and caffeine intake and breast cancer risk: an updated dose-response meta-analysis of 37 published studies. *Gynecol Oncol*. 129(3):620–9.
[287] Wang et al. (2016), full citation provided in footnote 206.
[288] Lafranconi et al. (2018), full citation provided in footnote 249.
[289] Harris HR, Bergkvist L, Wolk A (2015). An estrogen-associated dietary pattern and breast cancer risk in the Swedish Mammography Cohort. *Int. J. Cancer* 137: 2149–2154.

37,004 women from the Swedish Mammography Cohort. Coffee consumption was not associated with breast cancer risk in this study.

- Bamia et al. (2017)[290], referenced by NCA, was an abstract for a presentation at a meeting that does not contain sufficient information to evaluate the study. We also note that as a meeting abstract the study would not meet the IARC requirement for full consideration and summarization[291].

Most of the studies provided by CERT found no association or an inverse association between coffee consumption and breast cancer risk. Three studies, Trieu et al. (2017)[292], Yaghjyan et al. (2018)[293], and Arthur et al. (2018)[294], found positive associations in subgroups, but they were not confirmed by other large cohort studies, or showed internal inconsistencies with other study findings. OEHHA continues to find that IARC's conclusion that there is "*evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancers of the…female breast" remains consistent with the current evidence.

No changes to the proposed regulation were made based on this comment.

Comment 38 (CERT[295]): The commenter expresses concern about potential exposure misclassification from use of food frequency questionnaires and self-reporting and failure of the studies to adequately address cigarette smoking and dietary and other factors such as exercise and breastfeeding that may contribute to reduced breast cancer risk. The commenter also states, "The foregoing discussion shows that OEHHA's conclusion that consumption of coffee is protective against cancer in women is unfounded and is based on observational studies that are heavily confounded, that neither control nor adjust for multiple confounders that have been reported to reduce the risk of cancer in women, and that cannot appropriately serve as the basis for causal interpretation."

Response 38: Each of the studies reviewed by IARC[296] was evaluated for the possible roles of bias, including exposure misclassification, and confounding in the interpretation of study findings. IARC stated:

> "Evidence of the association between coffee consumption and risk of cancer of the breast was available from 23 cohort and 22 case-control studies. Most of the

[290] Bamia et al. (2017), full citation provided in footnote 250.
[291] IARC (2018), full citation provided in footnote 3, p. 12.
[292] Trieu et al. (2017), full citation provided in footnote 253.
[293] Yaghjyan et al. (2018), full citation provided in footnote 247.
[294] Arthur et al. (2018), full citation provided in footnote 245.
[295] CERT 18, pp. 140-153, 187-189
[296] IARC (2018), full citation provided in footnote 3, pp. 204-241.

> reviewed studies showed no association, and several reported statistically significant inverse associations between coffee intake and breast cancer overall or among subgroups of premenopausal or postmenopausal women."

As discussed in response to Comment 16, IARC lays out general criteria used for evaluating epidemiological studies for lack of evidence of carcinogenicity in the Preamble it includes in each Monograph Volume it publishes. OEHHA did not find any evidence that IARC applied its criteria improperly in evaluating the epidemiological evidence in the coffee Monograph.

No changes to the proposed regulation were made based on this comment.

Comment 39 (CERT[297]): The commenter expresses concern about confounding and breast cancer. "Several other factors have been reported to significantly reduce the risk of breast cancer, thereby confounding the association between coffee consumption and breast cancer."

> Cigarette smoking: "The inverse association of coffee consumption and breast cancer among postmenopausal women (and the absence of an association between coffee consumption and breast cancer generally) is likely due, at least in part, to confounding by cigarette smoking."
>
> Factors other than smoking: age, nutritional variables such as fiber intake, saturated fat intake, alcohol intake, tea intake, and total energy intake; coffee brewing methods; age at menarche, age at first full pregnancy, age at menopause.
>
> Factors reported to reduce breast cancer risk: dietary factors such as increased intake of calcium, carotenoids, dietary fiber, fatty acids (omega-3) and fish, flavan-3-ols, folate, fruit, the Mediterranean diet, soy, tea (especially green tea), vegetables, dietary/serum levels of beta-carotene, and vitamin B, C, D, and E, physical activity, and breastfeeding.

IARC concluded that "[t]here is evidence suggesting lack of carcinogenicity of drinking coffee in humans for cancers of the …female breast….". "However, nowhere in its discussion regarding coffee and breast cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence. Indeed, the Monograph doesn't even mention that meta-analyses have reported significantly

[297] CERT 18, pp. 129-140, 142, 176-178

decreased risks of breast cancer for multiple dietary factors…as well as physical activity and breastfeeding."

"The foregoing discussion shows that OEHHA's conclusion that consumption of coffee is protective against cancer in women is unfounded and is based on observational studies that are heavily confounded, that neither control nor adjust for multiple confounders that have been reported to reduce the risk of cancer in women, and that cannot appropriately serve as the basis for causal interpretation."

Response 39: In its review of the epidemiology studies of coffee consumption and risk of breast cancer, IARC took into consideration possible sources of confounding, and placed greater weight on studies that appropriately adjusted for confounding factors. IARC indicated limitations of studies that did not adjust for particular risk factors for breast cancer, such as reproductive history, hormones, and smoking. For each study evaluated, IARC[298] noted the covariates for which the studies controlled. For example, the prospective cohort study by Gierach et al. (2012)[299] controlled for age at entry, race/ethnicity, education, BMI, smoking status and dose, alcohol, proportion of total energy from fat, age at first live birth, menopausal hormone replacement therapy (HRT) use, history of breast biopsy, and family history of breast cancer in a first-degree relative, and the case-control study by Wu et al. (2003)[300] controlled for education, age at menarche, pregnancy, current BMI, total caloric intake, menopausal status, use of menopausal hormones, intake of soy, dark green vegetables, smoking history, alcohol intake, physical activity, and family history of breast cancer[301].

In its overall summary, IARC emphasized the most recent meta-analysis of nearly one million women and 50,000 breast cancer cases that indicated an inverse dose-response relationship (overall meta-RR = 0.97, 95% CI: 0.93–1.00, $p = 0.09$) (Jiang et al. 2013[302]). Statistically significant inverse associations were observed among postmenopausal women (meta-RR = 0.94, 95% CI: 0.8–0.99, $p = 0.02$), and among pre- and postmenopausal *BRCA1* mutation carriers (meta-RR = 0.69, 95% CI: 0.53–0.89, $p = 0.01$). This meta-analysis extracted risk estimates from each of the component studies that reflected the greatest degree of adjustment for potential confounders. In

[298] IARC (2018), full citation provided in footnote 3, pp. 204-241.
[299] Gierach GL, Freedman ND, Andaya A, Hollenbeck AR, Park Y, Schatzkin A et al. (2012). Coffee intake and breast cancer risk in the NIH-AARP diet and health study cohort. *Int. J. Cancer* 131(2):452–60.
[300] Wu AH, Yu MC, Tseng CC, Hankin J, Pike MC (2003). Green tea and risk of breast cancer in Asian Americans. *Int. J. Cancer* 106(4):574–9.
[301] IARC (2018), full citation provided in footnote 3, pp. 214, 228.
[302] Jiang et al. (2013), full citation provided in footnote 286.

additional analyses, the authors also conducted subgroup analyses by "adjustment (yes or no) for smoking and/or alcohol, BMI, total energy intake, physical activity, oral contraceptive use, postmenopausal hormone replacement therapy use, family history of breast cancer and history of benign breast disease"[303]. Adjusting for smoking and/or alcohol resulted in a slightly lower RR as compared with no adjustment (no adjustment meta-RR = 1.00, 95% CI: 0.93–1.07, p = 0.98; adjustment for smoking and/or alcohol meta-RR = 0.96, 95% CI: 0.93–1.00, p = 0.06). Other subgroup analyses were not different from the overall analysis. For example, adjustment for physical activity did not substantially change the results compared to the overall model (no adjustment for physical activity: meta-RR = 0.98, 95% CI: 0.94–1.02; adjustment for physical activity: meta-RR = 0.97, 95% CI: 0.91–1.02).

IARC's summary also emphasized that

> "[s]tudies published after this meta-analysis reported null or inverse associations overall and among postmenopausal women. An inverse association was also observed in the recent large cohort study [*Lukic et al*. (2016)]."[304]

This large cohort study, Lukic et al. (2016)[305], controlled for menopausal status, smoking status, education, BMI, physical activity level, alcohol consumption, number of children, age at first birth, use of HRT, and maternal history of breast cancer. For women drinking > 7 cups/day, there was an inverse, but not statistically significant, association (RR = 0.87, 95% CI: 0.71–1.06, p = 0.06)[306]. The other studies published after this meta-analysis also adjusted for a number of covariates. If a study did not appropriately adjust for covariates, IARC noted which covariates were not included.

The majority of studies reviewed by IARC and those published after the IARC review adjusted for cigarette smoking, alcohol intake, energy intake, menopausal status, physical activity, breastfeeding, and fat intake. A number of studies also adjusted for tea intake[307] (for example, Bhoo Pathy et al. 2010; Suzuki et al. 2004; Larsson et al. 2009; Boggs et al. 2010; Iwasaki et al. 2010; Oh et al. 2015; Rosenberg et al. 1985[308])

[303] *Ibid*.
[304] IARC (2018), full citation provided in footnote 3, p. 417.
[305] Lukic M, Jareid M, Weiderpass E, Braaten T (2016). Coffee consumption and the risk of malignant melanoma in the Norwegian Women and Cancer (NOWAC) Study. *BMC Cancer* 16:562.
[306] *Ibid.*
[307] IARC (2018), full citation provided in footnote 3.
[308] Bhoo Pathy et al. (2010), full citation provided in footnote 270; Suzuki Y, Tsubono Y, Nakaya N, Suzuki Y, Koizumi Y, Tsuji I (2004). Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. *Br. J. Cancer* 90(7):1361–3; Larsson SC, Akesson A, Wolk A (2009). Long-term dietary acrylamide intake and risk of epithelial ovarian cancer in a prospective cohort of Swedish women. *Cancer Epidemiol. Biomarkers Prev.* 18(3):994–

and/or fiber intake[309] (for example, Bhoo Pathy et al. 2010, 2015; Lukic et al. 2016[310]). These studies found risk estimates of similar magnitude to those that did not adjust for tea or fiber intake. Regarding coffee brewing method, most studies did not have this information.

OEHHA thus finds that it is unlikely that, overall, the null findings and inverse associations from the informative studies of coffee consumption and breast cancer are driven by uncontrolled confounding. Studies were conducted in multiple regions throughout the world (USA, Asia, and Europe) in populations with diverse dietary patterns and exercise habits. The fact that consistent results were seen across studies is indicative, in fact, of either null or inverse associations between coffee consumption and risk of breast cancer.

No changes to the proposed regulation were made based on this comment.

Colorectal cancer

Comment 40 (CERT[311]): CERT asserts that OEHHA claims that coffee prevents colorectal cancer: the IARC "Working Group judged the evidence to be inadequate for colorectal cancer … for reasons including inconsistency of findings across studies, inadequate control for potential confounding, potential for measurement error, selection bias or recall bias, or insufficient number of studies...OEHHA nevertheless asserts that 'coffee consumption has consistently been found to be protective for colorectal cancer risk' based on 'epidemiological studies published since IARC completed its literature search in 2016.' Initial Statement of Reasons at p. 7".

Response 40: The commenter is misstating what is in OEHHA's ISOR. In the ISOR, OEHHA states the IARC finding that there was moderate evidence that coffee drinking reduced the risk of colorectal adenoma, and OEHHA also notes that this lesion is a precursor lesion for colorectal cancer. According to IARC[312]

7; Boggs DA, Palmer JR, Stampfer MJ, Spiegelman D, Adams- Campbell LL, Rosenberg L (2010). Tea and coffee intake in relation to risk of breast cancer in the Black Women's Health Study. *Cancer Causes Control* 21(11):1941–8; Iwasaki M, Inoue M, Sasazuki S, Sawada N, Yamaji T, Shimazu T, et al.; Japan Public Health Center-Based Prospective Study Group (2010). Green tea drinking and subsequent risk of breast cancer in a population-based cohort of Japanese women. *Breast Cancer Res*, 12(5):R88; Oh JK, Sandin S, Ström P, Löf M, Adami HO, Weiderpass E (2015). Prospective study of breast cancer in relation to coffee, tea and caffeine in Sweden. *Int. J. Cancer* 137(8):1979–89; Rosenberg L, Miller DR, Helmrich SP, Kaufman DW, Schottenfeld D, Stolley PD, et al. (1985). Breast cancer and the consumption of coffee. *Am. J. Epidemiol.* 122(3):391–9.

[309] IARC (2018), full citation provided in footnote 3.

[310] Bhoo Pathy et al. (2010), full citation provided in footnote 270; Bhoo Pathy et al. (2015), full citation provided in footnote 267; Lukic et al. (2016), full citation provided in footnote 305.

[311] CERT 18, pp. 142-143

[312] IARC (2018), full citation provided in footnote 3, p. 424.

> "There is moderate evidence regarding the association between coffee drinking and risk of colorectal adenomas. An inverse association between coffee drinking and risk of colorectal adenomas was found in several studies; however, possible uncontrolled confounding and selection biases cannot be excluded."

On page 7 of the ISOR, OEHHA does report findings from studies on colorectal cancer that were published since IARC completed its review in 2016. OEHHA does not reach an overall conclusion that coffee protects against colorectal cancer, but simply states the fact that:

> "In epidemiological studies published since IARC completed its literature search in 2016, coffee consumption has consistently been found to be protective of colorectal cancer risk. Of 4 meta-analyses [referencing[313] Akter et al. 2016; Kashino et al. 2018; Wang et al. (2016); Vieira et al. (2017)], 2 prospective cohort studies [referencing[314] Nakamura et al. 2016; Groessl et al. 2016] and 5 case-control studies conducted in multiple countries with various methods [referencing[315] Budhathoki et al. 2015; Azzeh et al. 2017; Schmit et al. 2016; Nakagawa-Sendha et al. 2017; Ronco et al. 2017], almost all found significant inverse associations of coffee consumption and colorectal cancer. The exceptions were one meta-analysis [referencing Vieira et al. 2017] that found no association with coffee consumption and colorectal cancer, and one cohort study [referencing Groessl et al. 2016] that found an increase in colorectal cancer."

[313] Akter S, Kashino I, Mizoue T et al. (2016). Coffee drinking and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population. *Jpn J Clin Oncol* 46(8):781-787; Kashino I, Akter S, Mizoue T, Sawada N, Kotemori A, Matsuo K et al. (2018). Coffee drinking and colorectal cancer and its subsites: A pooled analysis of 8 chort studies in Japan. *Int J Cancer* 143(2):307-316; Wang et al. (2016), full citation provided in footnote 206; Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, Stevens C, Greenwood D, Norat T (2017). Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Ann Oncol* 28(8): 1788-1802.

[314] Nakamura T, Ishikawa H, Mutoh M, Wakabayashi K, Kawano A, Sakai T, Matsuura N (2016). Coffee prevents proximal colorectal adenomas in Japanese men: a prospective cohort study. *Eur J Cancer Prev* 25:388–394; Groessl EJ, Allison MA, Larson JC, Ho SB, Snetslaar LG, Lane DS, Tharp KM, Stefanick ML (2016). Coffee consumption and the incidence of colorectal cancer in women. *J. Cancer Epidemiol.* 2016:6918431.

[315] Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Tsugane S (2015). Coffee intake and the risk of colorectal adenoma: The colorectal adenoma study in Tokyo. *Int J Cancer*. 137(2):463-70; Azzeh FS, Alshammari EM, Alazzeh AY, Jazar AS, Dabbour IR, El-Taani HA, Obeidat AA, Katan FA, Tashtoush SH (2017). Healthy dietary patterns decrease the risk of colorectal cancer in the Mecca Region, Saudi Arabia: a case-control study. *BMC Public Health* 17(1):607; Schmit SL, Rennert HS, Rennert G, Gruber SB (2016). Coffee consumption and the risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 25(4):634-639; Nakagawa-Senda H, Ito H, Hosono S, Oze I, Tanaka H, Matsuo K (2017). Coffee consumption and the risk of colorectal cancer by anatomical subsite in Japan: Results from the HERPACC studies. *Int. J Cancer* 141(2):298-308; Ronco AL, De Stefani E, Lasalvia-Galante E, Mendoza B, Vazquez A, Sanchez G (2017). Hot infusions and risk of colorectal cancer in Uruguay: a case-control study. *Eur J Clin Nutr* 71:1429-1436.

Ultimately in 2016 IARC[316] found that "there is inadequate evidence in humans for the carcinogenicity of coffee drinking" for colorectal cancer, while also finding moderate evidence of an inverse association for colorectal adenoma, a precursor lesion for colorectal cancer.

No changes to the proposed regulation were made based on this comment.

Comment 41 (CERT[317]): CERT states:

> "Additionally, it is scientifically improper for OEHHA to consider only those studies published during the two-year period since IARC completed its literature search to conclude that coffee consumption is 'protective for colorectal cancer risk.' To properly render such a scientific conclusion, it is necessary to consider the entire body of scientific literature regarding consumption of coffee and colorectal cancer - not just those studies published during a two-year period. It is precisely such an analysis that Dr. Peter Infante did in preparing his July 2017 report … In that report, Dr. Infante appropriately considers all of the epidemiological studies regarding consumption of coffee and colorectal cancer that had been published by the summer of 2017 and concludes that those studies show "mixed" results, rather than any allegedly cancer-protective effect."

Response 41: The commenter is not correct that OEHHA considered only those studies published during the two-year period since IARC completed its literature search. The context of the presentation of these studies is discussed in response to Comment 40. CERT provided in its submissions Dr. Infante's July 2017 report[318]. After describing eight meta-analyses on the association of coffee consumption and risk of colorectal cancer, in which his descriptions for five studies report significant inverse associations, and the remainder report null associations, Dr. Infante hypothesizes:

> "The inverse relationship between coffee consumption and colorectal cancer may be due to confounding by factors that have been shown in meta-analyses to significantly reduce the risk of colorectal cancer and by other as yet unknown protective factors."[319]

[316] IARC (2018), full citation provided in footnote 3, p. 420.
[317] CERT 18, p. 143
[318] CERT 6, Exhibit B. Available at https://oehha.ca.gov/media/dockets/10976/11022-certs_submission_no._6_regarding_the_opinions_of_dr._peter_f._infante_regarding_epidemiologic_studies_regarding_coffee_and_cancer./certs_submission_no._6.pdf
[319] CERT 6, Exhibit B, p. 26

Thus, Dr. Infante, in his 2017 report, is recognizing observations of inverse associations, and postulating that they may be due to confounding.

As noted above in response to Comment 40, the ISOR acknowledged the IARC finding of inadequate evidence for the carcinogenicity of colorectal cancer, and reported on observations in studies since that finding in 2016. CERT in its comments reports on findings since the IARC review in its commentary on the ISOR in section V.D[320], although CERT confines its scope to those studies it found to report positive associations between coffee and cancer risk. We further address those findings in response to Comment 44 below.

Regarding colorectal adenoma, the studies cited by CERT do not specifically address colorectal adenoma, and do not provide new evidence that would add substantially to the body of evidence for which IARC found "moderate evidence of an association of coffee drinking with reduced risk of colorectal adenoma"[321]. Only one study they provided specifically looked at colorectal adenoma, and found an inverse association between coffee drinking and adenoma: Olsen and Kronborg (1993)[322] was a case-control study conducted in Denmark with 397 cases and 362 age- and sex-matched controls. This study found a statistically significant reduced risk of colorectal adenomas associated with coffee consumption.

No changes to the proposed regulation were made based on this comment.

Comment 42 (CERT; Melnick[323]): Regarding colorectal adenoma, Melnick states, quoting from IARC that:

> "An inverse association between coffee drinking and risk of colorectal adenomas was found in several studies; however, possible uncontrolled confounding and selection biases cannot be excluded."

Then Melnick writes:

> "IARC did not conclude that the Working Group found moderate evidence of an inverse association between coffee drinking and colorectal cancer!"

Response 42: OEHHA did not state that there was moderate evidence of an inverse relationship for colorectal *cancer*, but rather for colorectal *adenoma*, which is a precursor lesion for colorectal cancer. As noted in response to Comment 17, IARC has

[320] CERT 18, pp. 84-90
[321] Loomis et al. (2016), full citation provided in footnote 36.
[322] Olsen J, Kronborg O (1993). Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine. *Int. J. Epidemiol.* 22:398-402.
[323] CERT 18, pp. 162-169; Melnick, pp. 7-8

a system of categorizing evidence from human, experimental animal and mechanistic data. For direct evidence of cancer in humans or experimental animals, IARC uses the categories “sufficient”, “limited”, “inadequate evidence of carcinogenicity” or “evidence suggesting lack of carcinogenicity”. However, for indirect “mechanistic and other relevant data” IARC uses different categories: of “strong”, “moderate” and “weak”. The IARC guidance[324] on this is as follows:

> “Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physico-chemical parameters and analogous biological agents.”
>
> “The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as ‘weak’, **‘moderate’** or ‘strong’. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans.” [emphasis added]

In this particular case, IARC judged the evidence as “moderate” for an inverse relationship between coffee drinking and colorectal adenoma. Had IARC judged bias and confounding to have been ruled out with confidence, the evidence would have been judged by IARC to be “strong”.

No changes to the proposed regulation were made based on this comment.

Comment 43 (CERT[325]): “The inverse relationship between coffee consumption and colorectal cancer that has been reported in some studies may be due to confounding by factors that have been shown in meta-analyses to significantly reduce the risk of colorectal cancer and by other as yet unknown factors”, such as dietary factors, physical activity, vitamins, pharmaceuticals, and reproductive factors.

Response 43: As explained in the response to Comment 21, not all the listed factors would be considered confounders, and over-adjustment can potentially introduce bias. That said, IARC did not reach a conclusion of inverse association for colorectal cancer, and instead reached the conclusion that there was inadequate evidence of carcinogenicity for cancer of the colon.

[324] IARC (2018), full citation provided in footnote 3, p. 29.
[325] CERT 18, pp. 162-169

No changes to the proposed regulation were made based on this comment.

Comment 44 (CERT; NCA[326]): Regarding studies released subsequent to the IARC meeting, CERT reports:

> "Two epidemiological studies published since IARC completed its review have reported increased risks of colorectal cancers in association with consumption of coffee",

and briefly presents results from two cohort studies: Groessl et al. (2016)[327] and Zamora-Ros et al. (2018)[328].

NCA comments:

> "In our surveillance of the literature post-IARC (from 2016-2018) there have been 15 studies looking at the relationship between coffee and colon cancer. Nearly all of the studies found an inverse association with coffee consumption and risk of colorectal cancer."

NCA then shows tabulated conclusions and remarks for 15 epidemiology studies: three case-control studies – Amiano et al. (2018)[329], Schmit et al. (2016)[330], Nakagawa-Senda et al. (2017)[331]; three cohort studies – Groessl et al. (2016)[332], Gapstur et al. (2017)[333], Hu et al. (2018)[334]; six meta-analyses – Kashino et al. (2018)[335], Wang et al. (2016)[336], Akter et al. (2016)[337], Vieira et al. (2017)[338], Horisaki et al. (2018)[339], Gan et al.

[326] CERT 18, pp. 86-87, 142-162; NCA, pp. 20, 33-38
[327] Groessl et al. (2016), full citation provided in footnote 314.
[328] Zamora-Ros R, Cayssials V, Jenab M, Rothwell JA, Fedirko V, Aleksandrova K et al. (2018). Dietary intake of total polyphenol and polyphenol classes and the risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Eur. J. Epidemiol.* [Epub ahead of print]
[329] Amiano P, Molina-Montes E, Molinuevo A, Huerta JM, Romaguera D, Gracia E et al. (2018). Association study of dietary non-enzymatic antioxidant capacity (NEAC) and colorectal cancer risk in the Spanish Multicase-Control Cancer (MCC-Spain) study. *Eur J Nutr*. [Epub ahead of print.]
[330] Schmit et al. (2016), full citation provided in footnote 315.
[331] Nakagawa-Senda et al. (2017), full citation provided in footnote 315.
[331] Wang et al. (2016), full citation provided in footnote 206.
[332] Groessl et al. (2016), full citation provided in footnote 314.
[333] Gapstur et al. (2017), full citation provided in footnote 148.
[334] Hu Y, Ding M, Yuan C, Wu K, Smith-Warner SA, Hu FB, Chan AT, Meyerhardt JA, Ogino S, Fuchs CS (2018). Association between coffee intake after diagnosis of colorectal cancer and reduced mortality. *Gastroenterology* 154:916-926.
[335] Kashino et al. (2018), full citation provided in footnote 313.
[336] Wang et al. (2016), full citation provided in footnote 206.
[337] Akter et al. (2016), full citation provided in footnote 313.
[338] Vieira et al. (2017), full citation provided in footnote 313.
[339] Horisaki K, Takahashi K, Ito H, Matsui S (2018). A Dose-Response Meta-analysis of Coffee Consumption and Colorectal Cancer Risk in the Japanese Population: Application of a Cubic-Spline Model. *J. Epidemiol.* doi: 10.2188/jea.JE20170201.

(2017)[340]; one abstract[341]; one umbrella review – Grosso et al. (2017)[342]; and one review/reanalysis – Alicandro et al. (2017)[343], which cited a recent prospective cohort study, Nakamura et al. (2016)[344].

CERT, in its section VII - "OEHHA's claim that coffee prevents colorectal cancer" - describes results from studies reported after the IARC Monograph was released: a cohort study by Gunter et al. (2017)[345] and the following studies just mentioned: Groessl et al. (2016), Gan et al. (2017)[346], Wang et al. (2016), Akter et al. (2016), Nakagawa-Senda et al. (2017), Viera et al. (2017), Zamora-Ros et al. (2018), Horisaki et al. (2018). CERT also describes some studies that were published before the 2016 meeting that were not described in the IARC recent Monograph on coffee[347,348,349,350].

Response 44: OEHHA has reviewed the studies cited by CERT and NCA, and provides the following brief observations:

With regard to the meta-analyses and pooled analyses briefly described by NCA and/or CERT that were published after the 2016 IARC review:

- Wang et al. (2016) included 21 cohort studies in their analysis comparing highest versus lowest intake of coffee and colorectal cancer. They found no association with colorectal cancer or rectal cancer, and an inverse association with colon cancer (RR = 0.87, 95% CI = 0.78–0.96, *p* = 0.007).
- Akter et al. (2016)[351] included five cohort and nine case-control studies of populations in Japan. This study found no association of coffee consumption (highest vs lowest categories) with colorectal or colon cancer in the summary risk for cohort studies and an inverse association in the case-control studies.

[340] Gan Y, Wu J, Zhang S, Li L, Cao S, Mkandawire N et al. (2017). Association of coffee consumption with risk of colorectal cancer: a meta-analysis of prospective cohort studies. Oncotarget 8(12):18699-18711.
[341] Jarosz M, Rychlik E, Sekula W (2017). Coffee consumption and selected gastrointestinal cancers morbidity in Poland. *Ann. Nutr. Met.* 71 Supplement 2 (984). Poster.
[342] Grosso et al. (2017), full citation provided in footnote 251.
[343] Alicandro G, Tavani A, La Vecchia C (2017). Coffee and cancer risk: a summary overview. *Eur J Cancer Prev*. 26(5):424-432.
[344] Nakamura et al. (2016), full citation provided in footnote 314.
[345] Gunter MJ, Murphy N, Cross AJ, Dossus L, Dartois L, Fagherazzi G et al. (2017). Coffee drinking and mortality in 10 European countries: a multinational cohort study. *Ann. Intern. Med.* 167(4):236-247.
[346] Gan et al. (2017), full citation provided in footnote 340.
[347] Zhang B, Li X, Nakama H, Zhang X, Wei N, Zhang X, Zhang L (2002). A case-control study on risk of changing food consumption for colorectal cancer. *Cancer Invest.* 20(4):458-463.
[348] Shannon J, White E, Shattuck AL, Potter JD (1996). Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 5(7):495-502.
[349] Olsen and Kronborg (1993), full citation provided in footnote 322.
[350] Tavani A, Fioretti F, Franceschi S, Gallus S, Negri E, Montella M et al. (1999). Education, socioeconomic status and risk of cancer of the colon and rectum. *Int. J. Epidemiol.* 28(3):380-385.
[351] Akter et al. (2016), full citation provided in footnote 313.

- Horisaki et al. (2018)[352] analyzed this same data as analyzed by Akter et al. and conducted a dose-response meta-analysis to investigate risks with respect to specific exposure values. This study also found that coffee consumption was either not associated or weakly inversely associated with risk of colorectal cancer in pooled analyses.
- Vieira et al. (2017)[353] included 14 studies for colorectal cancer, 11 studies for colon cancer, and 15 studies for rectal cancer. Studies were prospective cohort, case-cohort, or nested case-control studies. Coffee was not statistically significantly associated with an increased risk for colorectal cancer, colon cancer, or rectal cancer.
- Kashino et al. (2018)[354] was a pooled analysis of eight cohort studies in Japan that included 320,322 participants, and was included in the ISOR. The authors reported that: "Coffee drinking was not materially associated with colorectal cancer risk in men or women (pooled HR 0.92, 95% CI 0.82–1.03 in men and pooled HR 0.90, 95% CI 0.76–1.07 in women). Analysis by subsite showed a lower risk of colon cancer among female drinkers of ⩾3 cups coffee/day (pooled HR 0.80, 95% CI 0.64–0.99). There was no such association in men. Coffee drinking was not associated with risk of rectal cancer in men or women. Results were virtually the same among never smokers except for an increased risk of rectal cancer associated with frequent coffee consumption. Coffee drinking may be associated with lower risk of colon cancer in Japanese women."
- Gan et al. (2017)[355] was a meta-analysis that included 19 prospective cohort studies. Coffee consumption was not associated with colorectal, colon, or rectal cancers in the high vs low coffee comparisons. When analyzed by cups of coffee per day, five or more cups per day were associated with decreased risk of colorectal cancer and four or more cups per day were associated with decreased risk of colon cancer.

With regard to the recent cohort or pooled cohort studies described by CERT or NCA:

- Gapstur et al. (2017)[356], briefly discussed by CERT and NCA, was a prospective cohort study that followed 922,896 Cancer Prevention Study-II participants from 1982 through 2012. Among non-smokers, coffee consumption was inversely associated with death from colorectal cancer (HR = 0.97; 95% CI: 0.95–0.99).

[352] Horisaki et al. (2018), full citation provided in footnote 339.
[353] Vieira et al. (2017), full citation provided in footnote 313.
[354] Kashino et al. (2018), full citation provided in footnote 313.
[355] Gan et al. (2017), full citation provided in footnote 340.
[356] Gapstur et al. (2017), full citation provided in footnote 148.

- Groessl et al. (2016)[357], briefly discussed by CERT and NCA, was noted in the ISOR as a positive cohort study[358]. This study was a prospective cohort within the Women's Health Initiative Observational Study of 83,778 women with a mean follow-up of 12.9 years. Moderate coffee consumption but not high coffee consumption was associated with an increased risk of colorectal cancer; the trend *p* value was 0.04. Coffee intake was not associated with colon, rectum, or rectosigmoid cancers. In subgroup analyses, moderate coffee consumption of drip coffee (HR = 1.20, 95% CI: 1.05–1.36) and high consumption of non-drip coffee (HR = 1.43, 95% CI: 1.01–2.02) were associated with increased risks of colorectal cancer.
- Zamora-Ros et al. (2018)[359], briefly discussed by CERT, was a prospective cohort study within the EPIC study that investigated the association between polyphenol consumption and colon cancer risk. It was not a study of coffee drinking per se. The cohort included 476,160 men and women with a mean follow-up of 14 years. Polyphenol intake was estimated using validated dietary questionnaires including questions about intake of coffee and other items containing polyphenols, and the Phenol-Explorer database. The study found that higher intakes of phenolic acids were associated with a lower risk of colon cancer in men and a higher risk of rectal cancer in women. They treated polyphenol exposure as indicative of coffee consumption. One limitation is the potential impact of residual confounding, since several lifestyle and other dietary factors related to colorectal cancer were different according to polyphenol intake.
- Gunter et al. (2017)[360], submitted by CERT, also used the EPIC cohort to analyze the association of coffee intake with colorectal cancer mortality. The study did not find significant differences in comparisons of coffee consumption for groups with different levels of consumption versus non-consumers, for either men or women. However, in women there was a statistically significant trend for increasing coffee consumption and mortality. There were no associations in men overall.
- Nakamura et al. (2016)[361], the study cited in a review[362] referenced by NCA, was a prospective cohort study of 307 participants that investigated the association of coffee consumption with recurrence of colorectal tumors in Japanese men. The risk of colorectal tumor recurrence was reduced in patients who consumed more than three cups of coffee per day compared with those who consumed no coffee and not associated when analyzed by subtype of colorectal cancer.

[357] Groessl et al. (2016), full citation provided in footnote 314.
[358] OEHHA (2018), full citation provided in footnote 2.
[359] Zamora-Ros et al. (2018), full citation provided in footnote 328.
[360] Gunter et al. (2017), full citation provided in footnote 345.
[361] Nakamura et al. (2016), full citation provided in footnote 314.
[362] Alicandro et al. (2017), full citation provided on page 343.

- Loftfield et al. (2018)[363], referenced by NCA in its discussion of all-multiple cancer sites, was a prospective cohort study that evaluated associations of coffee drinking with all-cause and cause-specific mortality in the UK Biobank. Coffee consumption was not associated with increased risk of death from colorectal cancer in multivariable-adjusted models.

With regard to recent case-control studies described by CERT or NCA:

- Nakagawa-Senda et al. (2017)[364], described by CERT and NCA, was a pooled analysis of two hospital-based case-control studies conducted in Japan in the time periods 1988-2000 and 2001-2005. Coffee consumption was measured by a self-administered questionnaire. A total of 2,696 cases and 13,480 controls were included. Overall, there was an inverse association of coffee consumption for the highest compared to the lowest categories. Subgroup analyses were either associated with a lower risk or were not statistically significant.
- Schmit et al. (2016)[365], referenced by NCA, was a population-based case-control study of 5,145 cases and 4,097 controls conducted in Israel that found an inverse association between coffee consumption and colorectal cancer. The inverse association was also observed for decaffeinated coffee consumption alone and for boiled coffee. There was a significant dose-response trend of decreasing risk with increasing coffee consumption for both colon and rectal cancers.

OEHHA notes that one limitation of case-control studies is that they assess diet after the onset of disease, and reported diets of people with colorectal cancers can be influenced by the disease[366].

Grosso et al. (2017)[367], a review referenced by NCA, stated that coffee was associated with a probable decreased risk of colorectal and colon cancers. Hu et al. (2018)[368], referenced by NCA, evaluated the association between coffee intake after diagnosis of colorectal cancer and mortality. This study did not assess the association between coffee consumption and risk of colorectal cancer. Amiano et al. (2018)[369], referenced by NCA, evaluated the association of dietary non-enzymatic antioxidant capacity and colorectal cancer risk. It did not evaluate coffee consumption independently. Jarosz et

[363] Loftfield et al. (2018), full citation provided in footnote 252.
[364] Nakagawa-Senda et al. (2017), full citation provided in footnote 315.
[365] Schmit et al. (2016), full citation provided in footnote 315.
[366] IARC (2018), full citation provided in footnote 3, p. 301.
[367] Grosso et al. (2017), full citation provided in footnote 251.
[368] Hu et al. (2018), full citation provided in footnote 334.
[369] Amiano et al. (2018), full citation provided in footnote 329.

al. (2017)[370], referenced by NCA, is an abstract for an article that has not been published in a peer-reviewed journal and cannot be adequately evaluated.

Of the older studies included in the CERT discussion of colorectal cancer that were not included in the IARC Monograph:

- Olsen and Kronborg (1993)[371] was a case-control study conducted in Denmark with 397 cases and 362 age- and sex-matched controls. This study found a statistically significantly reduced risk of colorectal adenomas with coffee consumption.
- Zhang et al. (2002)[372] was a hospital-based case-control study conducted in China with 102 cases and 99 controls. A food frequency questionnaire was administered by an interviewer about consumption during four time periods: current, 5, 10, and 20 years ago. This study did not find an association between coffee drinking and colorectal cancer.
- Shannon et al. (1996)[373] was a population-based case-control study that investigated the association between food groupings and adenocarcinoma of the colon. Coffee was not associated with colon cancer in men or women. This study is not considered informative because there were so few cases and controls (26-41 subjects per group).
- Tavani et al. (1999)[374] was a pooled analysis of two hospital-based case-control studies in Italy, the same data sets analyzed by Tavani et al. (1997)[375], but stratified by education and social class. Tavani et al. (1999) found a statistically significantly increased risk of colon cancer in participants who had more than 16 years of education and were in the high social class and drank > 2 cups of coffee per day. Tavani et al. (1997) did not stratify by education or social class, and found an inverse association of coffee consumption and colon cancer or colorectal cancer in participants who drank at least four cups of coffee per day.

Additionally, Klatsky et al. (1988)[376] was a prospective cohort study of 106,203 men and women in northern California that was included in the meta-analysis of Gan et al. (2017) but was not discussed in the IARC Monograph. Coffee consumption was not associated with colon or rectal cancer in men and women combined. The main focus of

[370] Jarosz et al. (2017), full citation provided in footnote 341.
[371] Olsen and Kronborg (1993), full citation provided in footnote 322.
[372] Zhang et al. (2002), full citation provided in footnote 347.
[373] Shannon et al. (1996), full citation provided in footnote 348.
[374] Tavani et al. (1999), full citation provided in footnote 350.
[375] Tavani A, Pregnolato A, La Vecchia C, Negri E, Talamini R, Franceschi S (1997). Coffee and tea intake and risk of cancers of the colon and rectum: a study of 3,530 cases and 7,057 controls. *Int J Cancer* 73:193–7.
[376] Klatsky AL, Armstrong MA, Friedman GD and Hiatt RA (1988). The relations of alcoholic beverage use to colon and rectal cancer. *Amer J. Epid.* 128:1007-1015.

the study was alcoholic beverage use, and it is not clear if the model for coffee consumption adjusted for other factors such as smoking.

IARC (2018) summarized the data regarding colorectal cancer as follows[377]:

> "Approximately 50 prospective cohort, case–control, and pooling studies have been conducted to evaluate the association between coffee drinking and cancer of the colorectum. Ten cohort studies that were considered to be the most informative, with case numbers in the hundreds to over one thousand, found null associations between coffee consumption and colorectal cancer. Three cohort studies found an increased risk of either colon or rectal cancer. A pooled analysis of 13 cohort studies of colon cancer (over 5600 cases) found no association. Two subsequent large cohort studies conducted in the USA and Europe found inverse and null associations of colorectal cancer with coffee drinking, respectively. The findings from case–control studies were mixed, with inverse associations in most studies and positive or null associations in others."

Nearly all studies published since the IARC 2016 meeting were null or found an inverse association of coffee consumption with colorectal cancer. A few studies reported positive findings, mostly in subgroup analyses. Ultimately, it appears that the evidence suggesting lack of carcinogenicity and inverse association has become stronger, but it would require careful weighing in the context of potential biases to diverge from IARC's finding of inadequate evidence of carcinogenicity for colorectal cancer.

No changes to the proposed regulation were made based on this comment.

Esophageal cancer

Comment 45 (CERT; NCA[378]): CERT discusses studies on esophageal cancer in the sub-section on meta-analyses under "Coffee consumption increases the risk of several cancers." CERT briefly highlights results from two meta-analyses – Zhang et al. (2018)[379] and Yu et al. (2011)[380] – and briefly describes two case-control studies,

[377] IARC (2018), full citation provided in footnote 3, p. 420.
[378] CERT 18, pp. 61-63; NCA, pp. 30-32
[379] Zhang J, Zhou B, Hao C (2018). Coffee consumption and risk of esophageal cancer incidence. *Medicine* 97:17.
[380] Yu et al. (2011), full citation provided in footnote 204.

Petrick et al. (2015)[381] and Filiberti et al. (2017)[382], that were not included in IARC (2018).

NCA tabulated conclusions and briefly commented on five studies published since the IARC meeting, noting that "the weight of the evidence suggest no association." The studies they commented on were the Zhang et al. (2018) meta-analysis noted above, a prospective cohort study by Lukic et al. (2018b)[383], a retrospective cohort study only reported as an abstract by Kambhampati et al. (2017)[384], and a cohort study by Gapstur et al. (2017)[385]. NCA also referenced the summary overview paper by Alicandro et al. (2017)[386] that included results from a meta-analysis.

Response 45: Here, the case-control and cohort studies are first discussed, followed by the meta-analyses.

Regarding the two case-control studies mentioned by CERT, neither were of coffee and esophageal cancer per se:

- Petrick et al. (2015)[387] measured isoflavones and esophageal cancer risk. The authors reported that coffee accounts for approximately 37% of the dietary sources of isoflavones. This study did not specifically evaluate coffee consumption, and for this reason is of limited relevance.

- Filiberti et al. (2017)[388] is a hospital-based case-control study that examined coffee consumption and the risk of Barrett's esophagus, a condition associated with an increased risk of esophageal cancer. The authors found an adverse effect "among patients who had stopped drinking coffee." They note, "Coffee or tea intakes could be indicative of other lifestyle habits with protective or adverse impact on esophageal mucosa". However, this study did not control for tobacco smoking, which is a known cause of esophageal cancer and a reported risk

[381] Petrick JL, Steck SE, Bradshaw PT, Trivers KF, Abrahamson PE, Engel LS et al. (2015). Dietary intake of flavonoids and oesophageal and gastric cancer: incidence and survival in the United States of America (USA). *Br. J. Cancer* 112(7):1291-1300.
[382] Filiberti RA, Fontana V, De Ceglie A, Blanchi S, Grossi E, Della Cassa D et al. (2017) Association between coffee or tea drinking and Barrett's esophagus or esophagitis: an Italian study. *Eur. J. Clin. Nutr.* 71(8):980-986.
[383] Lukic et al. (2018b), full citation provided in footnote 198.
[384] Kambhampati S, Luber B, Wang H, Meltzer SJ (2017). Risk factors for progression of Barrett's esophagus to high grade dysplasia and esophageal adenocarcinoma: A large retrospective cohort study (abstract). *Gastroenterology* 152:5 Supplement 1 (S455).
[385] Gapstur et al. (2017), full citation provided in footnote 148.
[386] Alicandro et al. (2017), full citation provided in footnote 343.
[387] Petrick et al. (2015), full citation provided in footnote 381.
[388] Filiberti et al. (2017), full citation provided in footnote 382.

factor for Barrett's esophagus[389], and also is associated with coffee drinking and thus is an important potential confounder.

Regarding the cohort studies NCA noted:

- The prospective study by Lukic et al. (2018b)[390] included 193,439 women from the Norwegian Women and Cancer Study and the Northern Sweden Diet Database Study. This study found no evidence of an association between coffee consumption and risk of esophageal cancer.
- The prospective cohort study, Gapstur et al. (2017)[391] followed 922,896 Cancer Prevention Study-II participants from 1982 through 2012. Among non-smokers (never and former smokers combined), coffee consumption was positively associated with esophageal cancer-related death in one coffee consumption group, those who drank ⩾six cups/day (HR = 1.25, 95%CI: 1.00–1.55). When stratified by smoking status, coffee consumption was not associated with esophageal cancer-related death in former smokers, but was associated in never smokers. The authors stated: "The association of coffee consumption with higher risk of esophageal cancer among nonsmokers in our study should be confirmed."
- Kambhampati et al. (2017)[392], referenced by NCA, was an abstract that did not contain sufficient information to evaluate the study, and thus will not be addressed further.

Regarding the meta-analyses on coffee and esophageal cancer cited by commenters:

- Zhang et al. (2018)[393], which both CERT and NCA briefly discussed, included 11 studies, all of which were included in the IARC (2018) Monograph. The analysis found that coffee consumption has a protective effect on esophageal cancer risk in East Asians and no association in Euro-Americans.
- Yu et al. (2011)[394], noted by CERT, included two studies (both of which were included in IARC (2018)), and reported an inverse association between coffee consumption and esophageal cancer.

[389] Cook MB, Shaheen NJ, Anderson LA, Giffen C, Chow WH, Vaughan TL, Whiteman DC, Corley DA (2012). Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. *Gastroenterology*. 142(4):744-53.
[390] Lukic et al. (2018b), full citation provided in footnote 198.
[391] Gapstur et al. (2017), full citation provided in footnote 148.
[392] Kambhampati et al. (2017), full citation provided in footnote 384.
[393] Zhang et al. (2018), full citation provided in footnote 379.
[394] Yu et al. (2011), full citation provided in footnote 204.

- Alicandro et al. (2017)[395], referenced by NCA, did not find a relationship between coffee consumption and risk of esophageal cancer.

Regarding the studies evaluated in the Monograph, the summary of IARC (2018) stated,

> "Virtually all of these studies observed no association between coffee drinking and the risk of cancer of the oesophagus. One cohort study from Japan observed an inverse association with borderline statistical significance. No notable differences were observed between squamous cell and adenocarcinomas of the oesophagus. The two most recent case–control studies observed decreased risk. Two meta-analyses also suggested no association between coffee intake and oesophageal cancer."

On that basis, IARC reached the conclusion of "inadequate evidence of carcinogenicity" for esophageal cancer.

Of the studies published after IARC's review, one large cohort study[396] found no association of coffee and esophageal cancer and another large cohort study of mortality from esophageal cancer[397] found a positive association between coffee drinking and esophageal cancer-related death in a high consumption group of never smokers, but not former smokers. This singular finding is inconsistent with the body of the evidence. IARC overall classified the evidence of carcinogenicity inadequate for coffee drinking for esophageal cancer. The current evidence does not provide the basis to draw a different conclusion regarding esophageal cancer.

No changes to the proposed regulation were made based on this comment.

Hematopoietic Cancers

Childhood Leukemia

Comment 46 (CERT; Smith; Melnick; Infante; CSPI; NCA[398]): CERT and some other commenters stated that coffee increases the risk of childhood leukemia from maternal consumption during pregnancy. They discuss individual case-control studies and/or cite

[395] Alicandro et al. (2017), full citation provided in footnote 343.
[396] Lukic et al. (2018b), full citation provided in footnote 198.
[397] Gapstur et al. (2017), full citation provided in footnote 148.
[398] CERT H1, transcript pp. 23-24, 39; CERT 18, pp. 53-55, 59-61; Smith, pp. 6-8; Melnick, p. 7; Infante, pp. 1-14; CSPI, pp. 5-6; NCA, pp. 9-11, 24

a pooled analysis of case-control studies, Milne et al. 2018[399], released after the IARC working group met. CERT also submitted a published corrigendum by Yan et al. 2016[400], correcting an earlier meta-analysis. This also was not available to the IARC working group when it reviewed coffee drinking in 2016.

> "The Milne et al. (2018) study results run counter to OEHHA's statement that coffee 'has not been found to increase the risk of any cancers.' " (Infante, p 12).

NCA laid out reasons for concluding the evidence for childhood leukemia is inconclusive and also raised issues with respect to the case-control studies:

> "…Another meta-analysis [Cheng et al. 2014[401]] suggested that different results can occur when participants recall coffee consumption habits from being interviewed versus answering questions on a questionnaire. .. 'positive association between coffee consumption and childhood ALL among studies using interviewing techniques, but not among studies using self-administered questionnaire. The contrast may [be] due to a consequence of information bias (mainly recall bias) …' " (NCA, p. 11)

Response 46: IARC's review of the epidemiologic studies of childhood leukemia included seven case-control studies (IARC excluded Peters et al. 1994[402]) and one meta-analysis. Cohort studies were not available for studying maternal coffee exposure and childhood leukemia in the offspring. A brief description of the set of case-control studies discussed by IARC is given below. Greater detail is available in the original papers and the IARC Monograph.

- Peters et al. 1994[403]: The authors reported no apparent association between maternal coffee drinking and childhood leukemia (data not shown), the study was not presented in sufficient detail for review, and the study was not given weight in the IARC analysis.

[399] Milne, E, Greenop KR, Petridou E, Bailey HD, Orsi L, Kang AY et al. (2018). Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the Childhood Leukemia International Consortium. *Cancer Causes Control* 29(6):539-550.
[400] Yan K, Xu X, Liu X, Wang X, Hua S, Wang C, Liu X (2016). Corrigendum: The Associations Between Maternal Factors During Pregnancy and the Risk of Childhood Acute Lymphoblastic Leukemia: A Meta-Analysis. *Pediatr. Blood Cancer* 63(5):953-4.
[401] Cheng J, Su H, Zhu R, Wang X, Peng M, Song J, Fan D (2014). Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: a metaanalysis. *Am J Obstet Gynecol* 210(2):151.e1-151.e10.
[402] Peters JM, Preston-Martin S, London SJ, Bowman JD, Buckley JD, Thomas DC (1994). Processed meats and risk of childhood leukemia (California, USA). *Cancer Causes Control* 5(2):195–202.
[403] *Ibid.*

- Ross et al. 1996[404]: This study started with 303 cases of leukemia diagnosed in infants less than one year of age, from three different case-control studies conducted in North America. The authors were investigating the hypothesis that maternal diet and medications that inhibit DNA topoisomerase II could play a role in infant leukemia. The authors re-contacted the mothers of the infants up to 10 years later to recruit them to the case-control study. This resulted in 84 matched sets of infants and population-based controls. For all childhood leukemias combined, a statistically significant dose-response relationship was observed with coffee consumption (p-value for trend = 0.04). Limitations noted by IARC included small sample size and selection bias, given the low participation rate (28% of the original cases).
- Petridou et al. (1997)[405] was a hospital-based case-control study conducted in Greece of 153 cases of childhood leukemia and 300 hospital-based controls, matched on age, sex and locale. No association was observed with maternal coffee consumption. Limitations noted by IARC included a lack of detail about control diagnosis or reason for hospitalization, all types of childhood leukemia were analyzed together, and there was a modest sample size. Also, exposure was categorized as only binary, so an exposure–response analysis was not possible.
- Milne et al. (2011)[406] was a population-based case-control study conducted in Australia of 337 cases and 697 controls matched on age, sex and state of residence. No association was observed between acute lymphoblastic leukemia and coffee consumption. Limitations included low participation among controls; only 51% of participating control mothers completed the food frequency questionnaire, compared to 81% of participating case mothers, raising the possibility of selection bias. Additionally, controls had higher socioeconomic status than the general population. The authors also noted the potential for recall bias and measurement error.
- Four case-control studies from France, which were conducted by the French institute INSERM (Institut National de la Santé et de la Recherche Médicale; in English, the French Institute of Health and Medical Research):

[404] Ross JA, Potter JD, Reaman GH, Pendergrass TW, Robison LL (1996).Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Children's Cancer Group. *Cancer Causes Control* 7(6):581-90.
[405] Petridou E, Trichopoulos D, Kalapothaki V, Pourtsidis A, Kogevinas M, Kalmanti M et al. (1997). The risk profile of childhood leukaemia in Greece: a nationwide case-control study. *Br. J. Cancer* 76(9):1241–7.
[406] Milne E, Royle JA, Bennett LC, de Klerk NH, Bailey HD, Bower C et al. (2011). Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study. *Cancer Causes Control* 22:207-218.

- Menegaux et al. (2005)[407]: 280 incident cases of leukemia and 288 hospital controls were collected from four cities in France (Lille, Paris, Lyon, Nancy) between 1995-1999. Exposure was ascertained through in-person interviews. Controls were mainly recruited from orthopedic departments. Increased risks of childhood leukemia overall and acute lymphocytic leukemia were associated with the highest categories of maternal coffee drinking during pregnancy.
- Menegaux et al. (2007)[408]: 472 cases and 567 population-based controls were collected from 14 metropolitan regions of France between 1995-1998. The participants of this study did not overlap with Menegaux et al. (2005). Exposure was ascertained from self-administered mail-in questionnaires. Statistically significant increases in childhood leukemia with maternal coffee consumption were not seen.
- Bonaventure et al. (2013)[409]: 764 cases and 1681 population-based controls were included. Cases were identified through the French National Registry of Childhood Hematopoietic Malignancies for the years 2003-2004. Coffee exposure was ascertained through telephone interviews. Statistically significant increased risks for all leukemia, acute lymphocytic leukemia and acute myeloid leukemia, were associated with mothers who drank two or more cups of coffee per day. Statistically significant dose-response trends were also observed.
- Orsi et al. (2015)[410]: included 747 acute lymphocytic leukemia and acute myeloid leukemia cases combined and 1421 population-based controls. Cases were identified through the French National Registry of Childhood Hematopoietic Malignancies for the years 2010 and 2011. Coffee exposure was ascertained through telephone interviews. The study was mostly null, although there was an elevated risk of acute lymphocytic leukemia of borderline statistical significance for more than two cups a day maternal coffee consumption. (The lower bound of the confidence interval included 1.0.)

[407] Menegaux F, Steffen C, Bellec S, Baruchel A, Lescoeur B, Leverger G et al. (2005). Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. *Cancer Detect. Prev*. 29(6):487–93.
[408] Menegaux F, Ripert M, Hémon D, Clavel J (2007). Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study. *Paediatr. Perinat. Epidemiol.* 21(4):293–9.
[409] Bonaventure A, Rudant J, Goujon-Bellec S, Orsi L, Leverger G, Baruchel A et al. (2013). Childhood acute leukemia, maternal beverage intake during pregnancy, and metabolic polymorphisms. *Cancer Causes Control* 24(4):783–93.
[410] Orsi L, Rudant J, Ajrouche R, Leverger G, Baruchel A, Nelken B et al. (2015). Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study. *Cancer Causes Control* 26(7):1003–17.

The studies used different methods to ascertain exposure, with two performing in-person interviews (Petridou et al. 1997[411], Menegaux et al. 2005[412]), three utilizing telephone interviews (Ross et al. 1996[413], Bonaventure et al. 2013[414], Orsi et al. 2015[415]), and two relying on mailed-in questionnaire responses (Menegaux et al. 2007[416]; Milne et al. 2011[417]). They also used different methods for identifying cases and controls. There was no overlap in the study populations.

When evaluating the overall evidence for childhood leukemia, IARC stated the following:

> "Seven case–control studies have reported on the association between maternal coffee consumption during pregnancy and the risk of childhood leukaemia. The Working Group considered that the earliest two studies were of limited quality due to low participation fractions and uninformative exposure categories [Ross et al. 1996; Petridou et al. 1997]. Four of the remaining studies were conducted in France by the same research group (with no overlap of study populations). The first of these was hospital based and reported an increased risk with a significant dose–response trend [Menegaux et al. 2005]. A second study by this team 2 years later used a population-based approach and reported an odds ratio slightly and non-significantly above unity [Menegaux et al. 2007]. The third French study showed an increased risk with a significant dose–response trend [Bonaventure et al. 2013], while the results of the fourth study were largely null [Orsi et al. 2015]. An Australian study found no evidence of an increased risk. The most recent meta-analysis of this association reported an overall increased risk for high levels of coffee consumption, but was limited by the fact that the highest exposure level varied widely across studies (from $\geqslant$ 4 times per week to $\geqslant$ 8 times per day) [Thomopoulos et al. (2015)]. The lack of consistency among the findings of the studies, particularly those conducted within the same country by the same group[418], led the Working Group to evaluate the evidence for this site as inconclusive."[419]

As noted in the Preamble to the IARC Monographs, "well conducted [meta-analyses] can be considered", whereas "all pertinent epidemiologic studies" are included and reviewed. When a meta-analysis is reviewed by an IARC Working Group, "the same

[411] Petridou et al. (1997), full citation provided in footnote 405.
[412] Menegaux et al. (2005), full citation provided in footnote 407.
[413] Ross et al. (1996), full citation provided in footnote 404.
[414] Bonaventure et al. (2013), full citation provided in footnote 409.
[415] Orsi et al. (2015), full citation provided in footnote 410.
[416] Menegaux et al. (2007), full citation provided in footnote 408.
[417] Milne et al. (2011), full citation provided in footnote 406.
[418] The case-control studies conducted by the same group in France that IARC is referring to are Menegaux et al. (2005), Menegaux et al. (2007), Bonaventure et al. (2013), and Orsi et al. (2015).
[419] IARC (2018), full citation provided in footnote 3, p. 418.

criteria for data quality [are] applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account."

With respect to the meta- and pooled- analyses:

- Yan et al. (2016)[420], submitted by CERT, is an update of Yan et al. (2015)[421], a meta-analysis that was excluded from consideration by IARC (2018) because it lacked methodological details and had excluded some relevant studies. Yan et al. (2016)[422] found an association of coffee consumption during pregnancy with childhood acute lymphoblastic leukemia (OR = 1.44, 95% CI: 1.07–1.92), using three of the four INSERM studies – Bonaventure et al. (2013); Menegaux et al. (2005); Menegaux et al. (2007) – and the early study by Ross et al. (1996) for which selection bias associated with low participation rate was a major concern (28% of original cases included). IARC noted that Yan et al. (2015) excluded some relevant studies, and that is still the case with its corrigendum, Yan et al. (2016).
- Thomopoulos et al. (2015)[423], discussed by IARC and CERT, included all seven published case-control studies described by IARC, and also combined unpublished raw data from additional studies (Clavel et al. (2005)[424] and Petridou et al. (2005)[425]) into the meta-analytic estimate. Clavel et al. (2005), also from INSERM, included a subset of cases and controls from Menegaux et al. (2005). The cited paper by Petridou et al. (2005) makes no mention of coffee, but the authors of Thomopoulos et al. (2015) state that raw data on maternal coffee consumption from the study was used in the analysis.
- Cheng et al. (2014), cited by CERT and NCA, relies on three INSERM studies (Bonaventure et al. 2013, Menegaux et al. 2005, Menegaux et al. 2007) and reached similar conclusions. In that analysis the single INSERM Bonaventure et al. (2013) study received 78% or more of the weight in the overall meta-analyses:

[420] Yan et al. (2016), full citation provided in footnote 400.
[421] Yan K, Xu X, Liu X, Wang X, Hua S, Wang C, et al. (2015). The associations between maternal factors during pregnancy and the risk of childhood acute lymphoblastic leukemia: A meta-analysis. *Pediatr. Blood Cancer* 62(7):1162–70.
[422] Yan et al. (2016), full citation provided in footnote 400.
[423] Thomopoulos TP, Ntouvelis E, Diamantaras AA, Tzanoudaki M, Baka M, Hatzipantelis E et al. (2015). Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. *Cancer Epidemiol*. 39(6):1047–59.
[424] Clavel J, Bellec S, Rebouissou S, Menegaux F, Feunteun J, Bonaiti-Pellie C et al. (2005). Childhood leukaemia, polymorphisms of metabolism enzyme genes, and interactions with maternal tobacco, coffee and alcohol consumption during pregnancy. *Eur. J. Cancer* 14:531–540.
[425] Petridou E, Ntouvelis E, Dessypris N, Terzidis A, Trichopoulos D, Childhood Hematology-Oncology Group (2005). Maternal diet and acute lymphoblastic leukemia in young children. *Cancer Epidemiol. Biomarkers Prev.* 14:1935–1939.

for coffee consumers versus non-consumers – 78% weight, low-to-moderate coffee consumption – 89% weight, and high coffee consumption – 84% weight.

- Milne et al. (2018)[426], discussed by all the Comment 46 commenters, was published after IARC (2018). It is a pooled analysis of data from the case-control studies discussed by IARC: the four French INSERM studies, the Australian Milne et al. (2011) study, as well as two relatively small sets of unpublished case-control data from studies conducted in Greece. Although the California Childhood Leukemia Study is noted as one of the studies included, the study contained no data on coffee consumption and contributes no cases and no controls to the pooled analysis. The unpublished Greek data were given less than 2% of the weight in the Milne et al. (2018) pooled-analysis of greater than two cups per day versus none, indicative of very limited contribution for these additional data. While the Milne et al. (2018) study added subjects, the additional contribution was small and contributed little overall compared to the studies already reviewed by IARC.

In this pooled analysis of case-control studies, data on maternal coffee intake were available for 2,552 cases and 4,876 controls. Coffee intake was converted into a continuous variable of cups per day and statistical models were adjusted for important covariates. Individual study data were combined to obtain pooled ORs and confidence intervals.

No association was observed with any maternal coffee consumption during pregnancy (OR=1.04, 95% CI: 0.94–1.16). For two types of leukemia, there was an increased risk with greater than two cups per day of maternal coffee consumption (versus none) for overall acute lymphoblastic leukemia (OR = 1.27, 95% CI: 1.09–1.48, *p* trend: 0.005) and for B cell ALL (OR = 1.28, 95% CI: 1.09–1.50, *p* trend: 0.007), but not T cell ALL. As noted earlier, the French studies weighed most heavily in the analysis, contributing 87% of the weight to the greater than two cups per day consumption level. When looking at the individual studies, the finding at the greater than two cups per day level was only significant for the Bonaventure et al. (2013) study.

Milne and colleagues acknowledge that:

> "… the generalizability of our findings may be limited by the fact that almost 76% of the cases included in the coffee analysis were contributed by French studies. It is not clear, however, why any association between coffee intake and ALL [acute lymphoblastic leukemia] risk would be different in other western populations."

[426] Milne et al. (2018), full citation provided in footnote 399.

> "…our pooled analysis lacked the statistical power to allow firm conclusions to be drawn, particularly regarding associations within subgroups, and the results should be interpreted with caution."

While Milne et al. (2018) reported a statistically significant increased risk of childhood acute lymphocytic leukemia associated with two cups per day of maternal coffee consumption, the limitations in the individual studies and the inconsistencies between the French studies included in this pooled analysis remain. Bonaventure et al. (2013) reported statistically significant increased risks of childhood leukemia; whereas, the similarly sized Orsi et al. (2015) study is largely null, even though both studies used telephone interviews to ascertain exposure and both used the French countrywide National Registry of Childhood Hematopoietic Malignancies to ascertain cases. Menegaux et al. (2005) found a suggestion of an increase in childhood leukemia with an increase in maternal coffee consumption during pregnancy, while the Menegaux et al. (2007) study, which included nearly double the number of cases and controls, did not find statistically significant increases in risk with maternal coffee consumption for all leukemia, acute lymphocytic leukemia or acute myeloid leukemia.

The inconsistencies noted in the French studies raise questions about whether information and recall bias can be ruled out. Milne et al. (2018) included only case-control studies, and recall bias is inherent to case-control studies. The issue of differential recall among case mothers remains despite a statement from Milne et al. (2018) to the contrary.

Several papers have discussed recall bias as an important issue in case-control studies in which mothers of children with cancer are asked to recall diet or other exposures during pregnancy after a child has a serious outcome like leukemia.

Linet et al. (2003)[427] discussed issues in exposure assessment in case-control studies of childhood cancer:

> "Interview data may be subject to reporting, recall, or rumination effects, because parents of children with cancer will expend extensive effort to remember exposures that are often forgotten or only partially remembered by parents of healthy children. If exposures (e.g., diet, physical activity, other habits) change subsequent to onset of childhood cancer, then it may be difficult for the parent to recall accurately the child's prediagnostic exposures in postdiagnostic interviews. .. In general, most efforts have relied on maternal interview, an approach fraught

[427] Linet MS, Wacholder S, Zahm SH (2003). Interpreting epidemiologic research: lessons from studies of childhood cancer. *Pediatrics* 112:218-232.

> with potential for misclassification and differential recall between cases and control subjects [cites Savitz 2001[428]]"[429].

Poletta et al. (2012) looked at this issue in terms of maternal exposure to medications and the risk of birth defects, and found there was a "high rate of false-positive results presumably caused by differential misclassification bias" in case-control designs because "mothers are more likely to recall medication exposure than are mothers of healthy controls with similar medication use"[430]. Previous papers have also discussed this issue[431].

Orsi et al. (2015), included in the Milne et al. (2018)[432] pooled analysis, ultimately acknowledged the difficulties posed by case control studies and noted:

> "The role of maternal coffee drinking in CL [childhood leukemia] remains unclear and should be investigated further in consortium analyses and in large birth cohort studies with exposure assessment more contemporaneous with the exposure, before the occurrence of the disease."

Therefore, bias, including maternal recall bias, remains an important consideration in studying childhood leukemia and coffee. All of the literature to date on the association between maternal coffee drinking and childhood leukemia come from case-control studies, where recall bias remains an important limitation. While some positive associations were observed in the meta- and pooled- analyses of case-control studies, these findings were nonetheless still driven by the work of one research group, and the studies produced by that group remain internally inconsistent, as noted by IARC. Therefore, bias, chance and confounding cannot be ruled out with reasonable confidence to make causal statements about childhood leukemia and coffee consumption.

No changes to the proposed regulation were made based on this comment.

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[428] Savitz DA (2001). Environmental exposures and childhood cancer: our best may not be good enough. *Am J Public Health* 91:562–567.
[429] Linet et al. (2003), full citation provided in footnote 427.
[430] Poletta FA, Lopez Camelo JS, Gili JA, Leoncini E, Castilla EE, Mastroiacovo P (2012). Methodological approaches to evaluate teratogenic risk using birth defect registries: advantages and disadvantages. *PLoS ONE* 7(10): e46626.
[431] See Wacholder S, McLaughlin JK, Silverman DT, Mandel JS (1992a). Selection of controls in case-control studies. I. Principles. *Am J Epidemiol* 135: 1019–1028; Wacholder S, Silverman DT, McLaughlin JK, Mandel JS (1992c). Selection of controls in case-control studies. III. Design options. *Am J Epidemiol* 135: 1042–1050; Wacholder S, Silverman DT, McLaughlin JK, Mandel JS (1992b) Selection of controls in case-control studies. II. Types of controls. *Am J Epidemiol* 135:1029–1041; Elwood M (2007). Critical appraisal of epidemiological studies and clinical trials. 3rd ed. Oxford; New York: Oxford University Press. Oxford Medical Publications; Infante-Rivard C, Jacques L (2000) Empirical study of parental recall bias. *Am J Epidemiol* 152: 480–486.
[432] Milne et al. (2018), full citation provided in footnote 399.

Comment 47 (Infante[433]): IARC did not follow its own procedure in its review of meta-analyses of maternal coffee consumption and childhood leukemia.

Response 47: OEHHA disagrees with the comment, as it appears that IARC applied the procedures outlined in its Preamble to the review of meta-analyses of maternal coffee consumption and childhood leukemia.

IARC reaches an independent conclusion based on its review of published data; therefore, meta-analyses are reviewed by IARC in detail only when considered informative. As noted in the Preamble to the IARC Monographs, "well conducted [meta-analyses] can be considered", whereas "all pertinent epidemiological studies" are included and reviewed. When a meta-analysis is reviewed by an IARC Working Group, "the same criteria for data quality [are] applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account."

No changes to the proposed regulation were made based on this comment.

Comment 48 (Infante; Smith[434]):

> **"**In its Monograph on Coffee IARC does not discuss the biological mechanisms that would explain the association between maternal consumption of coffee and childhood leukemia. However, biologically plausible mechanisms for the development of childhood leukemia from maternal consumption of coffee during pregnancy are available in the published literature. During the Phase 1 trial in *CERT v. Starbucks,* Professor Martyn T. Smith, one of the world's leading researchers regarding the causes of childhood leukemia, testified that "the most probable mechanism to explain [the association] is that the clastogenic chemicals within coffee, including acrylamide, cross into the fetus and cause genetic damage in the fetus of the type where there's chromosome breakage, which leads to chromosome translocations, which then develops into leukemia; See also Milne et al. (2011); Sörgel et al. (2002); Annola et al. (2008)"[435]. (Infante, p. 14)

[433] Infante, pp. 8-9
[434] Infante, p. 14; Smith, p. 7
[435] Milne et al. (2011), full citation provided in footnote 406; Sörgel F, Weissenbacher R, Kinzig-Schippers M, Hofmann A, Illauer M, Skott A, Landeersdorfer C (2002). Acrylamide: increased concentrations in homemade food and first evidence of its variable absorption from food, variable metabolism and placental and breast milk transfer in humans. *Chemother.* 48(6):267-274; Annola K, Karttunen V, Keski-Rahkonen P, Myllynen P, Segerbäck D, Heinonen S, Vähäkangas K (2008). Transplacental transfer of acrylamide and glycidamide are comparable to that of antipyrine in perfused human placenta. *Toxicol. Lett.* 182:50-56.

Response 48: Dr. Smith is hypothesizing a mechanism without reviewing the evidence on the mechanisms of action for coffee. The IARC Monograph on coffee reviewed the literature published on the genotoxicity of coffee and its ability to induce chromosomal damage. In fact, genotoxicity is one of the key characteristics of carcinogens reviewed in every IARC Monograph as explained in a paper by Dr. Smith and colleagues (Smith et al. 2016)[436].

The IARC Monograph on coffee reported:

> **"**There is *weak* evidence that coffee drinking is genotoxic. The few studies in humans that have reported chromosomal damage in coffee drinkers have limitations in study design or else present conflicting results. Some studies found protective effects of coffee drinking on oxidative DNA damage or strand breaks in lymphocytes; however, some studies showed no effect, or suggested that coffee drinking may be associated with genetic alterations in lymphocytes and sperm cells. In human cells, results in vitro are conflicting. Studies in rodents in vivo have shown no evidence that coffee induces chromosomal damage. Furthermore, many studies demonstrated protective effects of coffee towards genotoxicity induced by several carcinogens in many organs. There is some evidence in mammalian cells in vitro for induction of sister-chromatid exchanges after exposure to coffee; however, consistent negative findings were reported for micronuclei and in the comet assay.**"**

No changes to the proposed regulation were made based on this comment.

Comment 49 (CERT; Infante[437]):

> "Dr. Bayard estimated an increased risk of childhood leukemia (< 14 years of age) from maternal consumption of 1-2 cups of coffee per day during pregnancy of 19.5 cases per 100,000 births–-a substantial risk of childhood leukemia. This increased risk level clearly exceeds the *de minimis* risk level of the Prop 65." (Infante, p. 13)

Response 49: This unpublished quantitative risk estimate is based on the assumption that coffee causes childhood leukemia. However, as discussed above, the evidence is not sufficient to establish coffee as a risk factor for childhood leukemia.

[436] Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I (2016). Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. *Environ. Health Perspect*. 124(6):713-21.
[437] CERT 19, pp. 4-8; Infante, pp. 13-14, and Attachment to Infante: Statement of Stephen Bayard. Calculation for Increased Risk of Two Acute Childhood Leukemias Due to Maternal Coffee Drinking During Pregnancy, Infante pdf pp. 53-57

No changes to the proposed regulation were made based on this comment.

Adult leukemia and lymphoma

Comment 50 (CERT; NCA[438]): NCA briefly describes two prospective cohort studies published after the 2016 IARC meeting, by Ugai et al. (2017)[439] for lymphoma and multiple myeloma, and Ugai et al. (2018)[440] for leukemia, as well as a case-control study by Parodi et al. (2017a)[441] for lymphoma, a case-control study by Parodi et al. (2017b)[442] for leukemia, and a meta-analysis by Han et al. (2016)[443] for lymphoma. In addition, CERT, after noting the null result for the Han et al. study for lymphoma, reported on four case-control studies – the case-control study of Parodi et al. (2017a), Cocco et al. (2015)[444], Cerliani et al. (2016)[445], and Gong et al. (2000)[446]. CERT concluded

> "Therefore, the meta-analysis [by Han et al. 2016] based on case-control studies did not take into consideration four studies that demonstrate significantly elevated risks of NHL [non-Hodgkins lymphoma] in relation to coffee consumption. As such, it cannot be relied upon to make a determination of NHL risk in relation to coffee intake."

CERT also reported on the meta-analyses of Wang et al. (2016)[447] that was released after the IARC meeting.

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[438] CERT 18, pp. 70-71, 89; NCA, pp. 24-26
[439] Ugai T, Matsuo K, Sawada N, Iwasaki M, Yamaji T, Shimazu T et al. (2018). Coffee and green tea consumption and subsequent risk of acute myeloid leukemia and myelodysplastic syndromes in Japan. *Int. J. Cancer* 142:1130-1138.
[440] Ugai T, Matsuo K, Sawada N, Iwasaki, Yamaji T, Shimazu T et al. (2017). Coffee and green tea consumption and subsequent risk of malignant lymphoma and multiple myeloma in Japan: The Japan Public Health Center-based Prospective Study. *Cancer Epidemiol. Biomarkers Prev.* 26(8):1352-1356.
[441] Parodi S, Merlo FD, Stagnaro E (2017a). Coffee consumption and risk of non-Hodgkin's lymphoma: evidence from the Italian multicentre case-control study. *Cancer Causes Control* 28(8):867-876.
[442] Parodi S, Merlo FD, Stagnaro E, on behalf of the Working Group for the Epidemiology of Hematolymphopoietic Malignancies in Italy (2017b). Coffee and tea consumption and risk of leukemia in an adult population: A reanalysis of the Italian multicenter case-control study. *Cancer Epidemiol.* 47:81-87.
[443] Han T, Li J, Wang L, Xu H (2016). Coffee and the Risk of Lymphoma: A Meta-analysis Article. *Iran. J. Public Health* 45(9):1126-1135.
[444] Cocco P, Zucca M, Sanna S, Satta G, Angelucci E et al. (2015). Interaction between dietary and lifestyle risk factors and N-acetyltransferase polymorphisms in B-cell lymphoma etiology. *J. Environ. Anal. Toxicol.* 5(5):1000315.
[445] Cerliani MB, Pavicic W, Gili JA, Klein G, Saba S, Richard S (2016). Cigarette smoking, dietary habits and genetic polymorphisms in *GSTT1*, *GSTM1* and *CYP1A1* metabolic genes: A case-control study in oncohematological diseases. *World J. Clin. Oncol.* 7(5):395-405.
[446] Gong Y (2000). Pulp and Paper Industry Emissions and Non-Hodgkin's Lymphoma Risk. *Queen's University* Kingston, Ontario, Canada [Masters' Thesis].
[447] Wang et al. (2016), full citation provided in footnote 206.

Response 50:

Neither meta-analysis found an association between coffee drinking and lymphoma:

- Han et al. (2016)[448], briefly discussed by CERT and NCA, concluded that there was not sufficient evidence to support an association between coffee consumption and risk of lymphoma. This meta-analysis included seven studies, five of which were reviewed by IARC (2018). Ward et al. (1994)[449] and Matsuo et al. (2001)[450] were not reviewed by IARC (2018). Ward et al. (1994) was a population-based case-control study on dietary factors and risk of NHL in men and women living in Nebraska. This study had fewer than 60 cases per group. Matsuo et al. (2001) was a hospital-based case-control study in Japan that did not find any association between coffee consumption and malignant lymphoma.
- Wang et al. (2016)[451], provided by CERT, did not find an association between coffee intake and lymphoma. All three studies included in the meta-analysis were evaluated in IARC (2018).

Regarding the cohort studies referenced by NCA:

- Ugai et al. (2017)[452] included 95,807 subjects from the Japan Public Health Center-based Prospective Study for an average follow-up of 18 years. Coffee consumption was not associated with risk of malignant lymphoma or multiple myeloma in either sex.
- Ugai et al. (2018)[453] analyzed the Ugai et al. (2017) cohort and found no association of coffee consumption with acute myeloid leukemia or myelodysplastic syndromes in men or women.

Regarding the case-control studies CERT indicated were missing from the Han et al. (2016) meta-analysis:

- Cerliani et al. (2016)[454], provided by CERT, was a hospital-based case-control study in Argentina that analyzed the association between oncohemotological diseases and polymorphisms, dietary habits and smoking. Data regarding

[448] Han et al. (2016), full citation provided in footnote 443.
[449] Ward MH, Zahm SH, Weisenburger DD, Gridley G, Cantor KP, Saal RC, Blair A (1994). Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States).*Cancer Causes Control* 5:422-32.
[450] Matsuo K, Hamajima N, Hirose K, Inoue M, Takezaki T, Kuroishi T, Tajima K (2001). Alcohol, smoking, and dietary status and susceptibility to malignant lymphoma in Japan: Results of a hospital-based case-control study at Aichi Cancer Center. *Jpn. J. Cancer Res.* 92:1011-1017.
[451] Wang et al. (2016), full citation provided in footnote 206.
[452] Ugai et al. (2017), full citation provided in footnote 440.
[453] Ugai et al. (2018), full citation provided in footnote 439.
[454] Cerliani et al. (2016), full citation provided in footnote 445.

dietary habits were collected via a survey that was not validated and only included information about current consumption. The study found that consumption of one or more cups/day of coffee compared to <one cup/day was associated with an increased risk of combined oncohemotological diseases (acute lymphoblastic leukemia, acute myeloblastic leukemia, chronic lymphoblastic leukemia, chronic myeloblastic leukemia, multiple myeloma, Hodgkin lymphoma, and NHL) (OR = 1.77, 95% CI: 1.03–3.03). Models were only adjusted for age, sex, and educational level. This study was also limited by the small number of cases and controls who drank >one cup/day (n = 35, 51, respectively).

- Cocco et al. (2015)[455]: This population-based case-control study investigated the interaction between N-acetyltransferase polymorphisms and exposure to coffee and other dietary and lifestyle risk factors in Italy. Coffee intake was not associated with risk of lymphoma.
- Parodi et al. (2017a)[456] was a population-based case-control study that evaluated the association between coffee consumption and the risk of NHL in Italy. The study found an increased risk of B cell lymphoma among heavy coffee drinkers. There was not a clear dose-response trend. In B cell lymphoma subgroup analyses, heavy coffee drinkers had an increased risk of follicular lymphoma. The risk increased with years of exposure and was more elevated among current smokers. There were very few subjects who were not habitual coffee drinkers. Two other Italian case-control studies[457,458] did not find statistically significant increased risks of coffee consumption and NHL. Studies conducted in India[459] and the US[460] found either no association or inverse associations. The authors suggested that coffee drinking may be associated with one or more lifestyle factors that are true risk factors for NHL. This analysis only took into account the effect of tobacco smoking since no information on other factors potentially associated with NHL risk was available.
- Gong (2000)[461], mentioned by CERT, was a thesis for a master's degree that was not published in a peer-reviewed journal, and therefore will not be discussed further here.

[455] Cocco et al. (2015), full citation provided in footnote 444.
[456] Parodi et al. (2017a), full citation provided in footnote 441.
[457] Franceschi S, Serraino D, Carbone A, Talamini R, La Vechhia C (1989). Dietary factors and non-Hodgkin's lymphoma: a case–control study in the northeastern part of Italy. *Nutr. Cancer* 12:333–341.
[458] Tavani A, Negri E, Franceschi S, Talamini R, La Vecchia C (1994). Coffee consumption and risk of non-Hodgkin's lymphoma. *Eur. J. Cancer Prev.* 3:351–356.
[459] Balasubramaniam G, Saoba S, Sarade M, Pinjare S (2013) Case–control study of risk factors for Non-Hodgkin lymphoma in Mumbai, India. *Asian Pac. J. Cancer Prev.* 14:775–780.
[460] Ward et al. (1994), full citation provided in footnote 449.
[461] Gong (2000), full citation provided in footnote 446.

Parodi et al. (2017b)[462], referenced by NCA, was a population-based case-control study in Italy that included 1,771 controls and 651 leukemia cases. Coffee consumption was not associated with any type of leukemia (acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, and chronic lymphoid leukemia).

The IARC (2018) summary stated, "The sparse evidence available for [lympho-haematopoietic cancer in adults] did not permit conclusions to be drawn." There is not enough information from these additional studies to draw further conclusions.

No changes to the proposed regulation were made based on this comment.

Comment 51 (CERT[463]): "The effect of coffee consumption on certain types of cancer has not been well studied, including adult leukemia and lymphoma. This is a critical gap in the scientific evidence, because exposures to other chemicals that are metabolized to epoxide intermediates by CYP2E1, the same human enzyme that metabolizes acrylamide to the DNA-reactive epoxide intermediate glycidamide, are associated with increased risk of leukemia and/or lymphomas in humans."

Response 51: As explained in the responses to Comments 26-29 above, coffee is a complex mixture that contains acrylamide and other carcinogens, as well as chemicals with cancer chemopreventive properties. A conclusion cannot be drawn regarding the association between coffee drinking and adult lympho-hematopoietic cancers due to the sparse evidence available[464].

However, it is notable that, as reviewed by IARC, exposure to coffee resulted in significant dose-related reductions in lymphosarcoma incidence at several organ sites in studies in mice[465]. The reductions occurred in both male and female mice, and were highly significant. In these studies, lymphosarcomas were "malignant tumors of lymphatic tissue with different morphological manifestations". The studies did not provide any details about the cytologic and histologic features of the lymphoid cell types to determine the specific type of lymphoma. "Lymphoproliferative disease in the mouse closely resembles that of humans"[466], and these tumors may be analogous to lymphomas in humans. Nonetheless, in evaluating the overall mixture of coffee, there are not sufficient data to reach conclusions about human adult leukemia and lymphoma. IARC stated:

[462] Parodi et al. (2017b), full citation provided in footnote 442.
[463] CERT 18, p. 33
[464] IARC (2018), full citation provided in footnote 3, p. 420.
[465] Stalder R, Bexter A, Würzner HP, Luginbühl H (1990). A carcinogenicity study of instant coffee in Swiss mice. *Food Chem Toxicol*. 28(12):829–37.
[466] Pattengale PK (1990). Classifications of mouse lymphoid cell neoplasms. In: Jones T.C., Ward J.M., Mohr U., Hunt R.D. (eds) Hemopoietic System. Monographs on Pathology of Laboratory Animals. Springer, Berlin, Heidelberg, pp. 137-143.

> "Associations between coffee drinking and … cancers at several other sites – including … lympho-haematopoietic cancer in adults … were examined in only a few studies … The sparse evidence available for these cancers did not permit conclusions to be drawn."

No changes to the proposed regulation were made based on this comment.

Laryngeal cancer

Comment 52 (CERT[467]): CERT briefly describes in the section "Coffee consumption increases the risk of several cancers" one case-control study by Sokic et al. (1994)[468] that was not included in the IARC Monograph (IARC 2018). CERT also reported on four meta-analyses, one of which, Ouyang et al. (2014)[469], was not discussed by IARC.

Response 52: The case-control study, Sokic et al. (1994)[470], did not adjust for smoking, an important risk factor for laryngeal cancer, and is, therefore biased and not informative. The meta-analysis, Ouyang et al. (2014)[471], found no significant association of coffee consumption with laryngeal cancer risk. Of note, this analysis included some studies that did not adjust for cigarette smoking, and therefore is biased and of limited use.

IARC (2018) summarized the evidence as follows:

> "Associations between coffee drinking and cancer of the larynx were evaluated in seven case–control studies, including a large pooled analysis, and one cohort study. The results of these studies were inconsistent. Statistically significantly increased risks were observed in four case–control studies, but none of these studies had adequately controlled for smoking and alcohol use. No evidence of an association was observed in studies that tightly controlled for smoking and alcohol drinking, or in the pooled analysis of case–control studies. No evidence of excess risk of laryngeal cancer among coffee drinkers was observed in the prospective cohort."

The additional studies provided do not allow further conclusions to be drawn.

[467] CERT 18, pp. 65-67
[468] Sokić SI, Adanja BJ, Marinković JP, Vlajinac HD (1994). Case-control study of risk factors in laryngeal cancer. *Neoplasma* 41(1):43-47.
[469] Ouyang Z, Wang Z, Jin J (2014). Association between tea and coffee consumption and risk of laryngeal cancer: a meta-analysis. *Int. J. Clin. Exp. Med.* 7(12):5192.
[470] Sokić et al. (1994), full citation provided in footnote 468.
[471] Ouyang et al. (2014), full citation provided in footnote 469.

No changes to the proposed regulation were made based on this comment.

Liver Cancer

Comment 53 (CERT[472]): The commenter states that a major limitation of the studies regarding coffee consumption and liver cancer is their inability to control for confounding factors. Specifically, CERT states,

> "Although most epidemiologic studies regarding coffee consumption and liver cancer report inverse associations, these studies are potentially grossly confounded by liver disease, especially Hepatitis B and C viruses which are known causes of liver cancer."
>
> "Additionally, IARC does not indicate that the studies adjusted for any confounders of liver cancer other than smoking and alcohol consumption, although many other factors have been associated with increased risks of liver cancer, including aflatoxins, androgenic (anabolic) steroids, betel quid, chronic liver disease, cyanotoxins, DDT, dichloromethane, 1,2- dichloropropane, estrogen-progestogen contraceptives, gamma radiation, HIV type 1, inorganic arsenic, obesity, contaminated (road, ditch and river) water, schistosome japonicum, trichloroethylene, vinyl chloride, x-radiation, and a few factors have been associated with decreased risks: green tea, tea, uncontaminated water."
>
> "Critically, the studies neither control nor adjust for multiple factors that have been reported to significantly decrease the risk of liver cancer in observational epidemiologic studies and meta-analyses, including the Mediterranean diet and other healthy dietary patterns, dietary fiber, vegetables, fish, tea, ginseng, various other dietary factors, trace elements and vitamins, medications, hormone replacement therapy and reproductive factors."
>
> "Nowhere in its discussion of coffee and liver cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence…OEHHA needs to resolve the impact of bias and confounding on reported liver cancer risk before accepting the observations as causally related to coffee."

[472] CERT 18, pp. 104-121, 171-174

Response 53: Most of the factors identified in the comment are not associated with the causal factor (coffee) and do not meet the criterion for confounding (See also Comment 21). As noted in the IARC Preamble, which provides guidance used by IARC Working Groups in their reviews, and is included in the front material for IARC Monograph Volume 116 (p. 17):

> "Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease."

None of the factors mentioned in the comment as being associated with decreased risk have been recognized as known protective factors for liver cancer. For example, the only interventions established by the National Cancer Institute as having adequate evidence of decreased risk of hepatocellular carcinoma are HBV vaccination, treatment for chronic HBV infection, and availability of food not contaminated with aflatoxin B1[473].

IARC's review that led to a determination of inverse association between coffee drinking and risk of liver cancer was attentive to hepatitis status, liver disease, and other possible confounders. As stated in the IARC Monograph,

> "All cohort studies adjusted for smoking and alcohol intake and, where possible, for hepatitis virus infection status and diabetes. All cohort studies observed inverse associations, which were statistically significant in most studies. Separate analyses by sex and by hepatitis C virus and/or hepatitis B virus infection status yielded similar results. Most case-control studies also observed inverse or null associations"[474].

Thus, inverse associations were also found when the analyses were restricted to groups with hepatitis virus infection. The covariates/confounders considered in each study are listed in Tables 2.5 and 2.6 of the IARC Monographs. The strengths and limitations in the factors adjusted for were noted.

No changes to the proposed regulation were made based on this comment.

[473] National Cancer Institute (2018). PDQ Liver (Hepatocellular) Cancer Prevention. PDQ® Screening and Prevention Editorial Board. Bethesda, MD: National Cancer Institute. Updated 08/02/2018. Available at: https://www.cancer.gov/types/liver/hp/liver-prevention-pdq.
[474] IARC (2018), full citation provided in footnote 3, p. 417.

Comment 54 (CERT[475]): CERT states that another major limitation of the studies regarding coffee consumption and liver cancer is reverse causation. CERT states, "People who have liver disease often can't drink coffee because of its acidity and their inability to metabolize caffeine and other constituents of coffee due to their underlying liver disease. So they either reduce their consumption on their own or because their doctors tell them to reduce coffee intake. Thus, the inverse association between coffee consumption and liver cancer is likely due to confounding by liver disease and reverse causation, the decreased risk of liver cancer being reflective of decreased (rather than increased) coffee consumption."

Response 54: It is unlikely that the inverse effects between coffee consumption and liver cancer found by IARC were due to reverse causation. Prospective studies inherently avoid a potential role of reverse causation (i.e., a reduction in the intake of coffee among liver cancer/chronic liver disease cases because of clinical symptoms of the disease)[476], since these studies enroll healthy individuals, assessing coffee consumption at enrollment, and assess health outcomes years later. Several cohort studies conducted sensitivity analyses excluding the first two years of follow-up and found similar results to the full analysis[477]. Excluding the first two years of follow-up would have the effect of removing cases with underlying liver disease at the time of enrollment when coffee consumption was measured. In addition, cohort studies that measured coffee intake at baseline and then again during follow-up questionnaires demonstrated results that were consistent with other studies. For example, the prospective cohort study by Lai et al. (2013)[478] obtained follow-up questionnaires periodically throughout the study and conducted lag analyses to account for changes in coffee consumption over time. They found a significant inverse association between consumption of ⩾four cups/day compared to >0 – <one cup/day and liver cancer (RR = 0.53, 95% CI: 0.30 – 0.95, *p* trend = 0.0007). These results were similar to those of the prospective cohort study by Bamia et al. (2015) that also found an inverse association (RR = 0.28, 95% CI: 0.16–0.50, *p* trend < 0.001).

Further, in case-control studies in which coffee consumption was assessed prior to developing the disease or any symptoms related to the disease inverse associations

[475] CERT 18, pp. 109-112, 172-174
[476] Bravi et al. (2017), full citation provided in footnote 123.
[477] For example, Bamia C, Lagiou P, Jenab M, Trichopoulou A, Fedirko V, Aleksandrova K et al. (2015). Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: multi-centre, prospective cohort study. *Int J Cancer*, 136(8):1899–908.
[478] IARC (2018), full citation provided in footnote 3, pp. 192-193.

were observed. For example, the population-based case-control study by Tanaka et al. (2007) obtained information on coffee use 10 years before liver cancer and found similar results compared to coffee consumption during the previous 1-2 years (previous 1-2 years: OR = 0.10, 95% CI: 0.04–0.24, *p* trend < 0.001; previous 10 years: OR = 0.22, 95% CI: 0.11–0.43, *p* trend < 0.001)[479].

IARC addressed this issue by explaining, "A major strength of cohort studies in nutritional epidemiology is the ability to demonstrate a temporal relationship between dietary exposure and cancer risk, as all dietary assessments are completed before diagnosis. This mitigates concerns related to recall bias and reverse causation. However, a limitation of many cohort studies is that exposures are often measured only once, usually during enrolment, whereas cancer cases develop over a long period of time. In the case of coffee consumption, however, there is a high correlation between successive measurements taken over time."[480]

No changes to the proposed regulation were made based on this comment.

Comment 55 (CERT[481]): The inverse association between coffee consumption and liver cancer may be due to exposure misclassification and/or other types of misclassification. CERT cites several examples from studies that discuss misclassification:

1) Misclassification of long-term exposure status could result from having only a single, self-reported measurement at study baseline, which does not account for the within-person variability over time (examples cited: Petrick et al. 2015[482]; Setiawan et al. 2015[483]; Inoue et al. 2005, 2009[484]; Hu et al. 2008[485]; Montella et al. 2007[486]; Tanaka et al. 2007[487]; Wakai et al. 2007[488]).

[479] IARC (2018), full citation provided in footnote 3, pp. 194, 199-200.
[480] IARC (2018), full citation provided in footnote 3, pp. 57-58.
[481] CERT 18, pp. 121-124
[482] Petrick et al. (2015), full citation provided in footnote 381.
[483] Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE (2015). Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US Multiethnic Cohort. *Gastroenterology* 148(1):118-125.
[484] Inoue et al. (2005), full citation provided in footnote 152; Inoue M, Kurahashi N, Iwasaki M, Shimazu T, Tanaka Y, Mizokami M, Tsugane S (2009). Effect of coffee and green tea consumption on the risk of liver cancer: cohort analysis by hepatitis virus infection status. *Cancer Epidemiol. Biomarkers Prev*. 18(6):1746-1753.
[485] Hu et al. (2008), full citation provided in footnote 151.
[486] Montella M, Polesel J, La Vecchia C, Maso LD, Crispo A, Crovatto M et al. (2007). Coffee and tea consumption and risk of hepatocellular carcinoma in Italy. Int. J. Cancer 120(7):1555-1559.
[487] Tanaka et al. (2007), full citation provided in footnote 156.
[488] Wakai K, Kurozawa Y, Shibata A, Fujita Y, Kotani K, Ogimoto I et al. (2007). Liver cancer risk, coffee, and hepatitis C virus infection: a nested case-control study in Japan. *Br. J. Cancer* 97(3):426-428.

2) Significant imprecision is a fact of life in dietary assessment, particularly when carried out retrospectively where the magnitude of errors may be different between cases and controls (example cited: Jenab and Boffetta 2010[489]).
3) Primary liver cancer cases identified on the basis of death certifications alone without confirmation by medical records might have a possibility of misclassifying secondary metastasis to the liver as primary liver cancer (example cited: Shimazu et al. 2005[490]).
4) Each study presented coffee consumption in different units (cups/week, cups/day, days/week, drinks/day, times/week). Therefore, differential misclassification could bias the results (examples cited: Sang et al. 2013[491]).

Response 55: For each study evaluated, IARC specifically considered the possibility of misclassification of exposure or outcome. Concerns about misclassification were noted in the limitations of the particular study. With respect to the examples CERT cites, OEHHA notes as follows:

1) If misclassification due to evaluation by a single measurement at baseline had occurred, it would likely have been nondifferential and would likely underestimate the results, because both the cases and controls would likely not have been different[492].
2) This comment refers to a form of differential misclassification called recall bias in which cases may recall their exposures differently than controls. This can bias the risk estimate in either direction. The study referred to by the commenter is an editorial on the application of glycemic index and glycemic load in observational studies and association with hepatocellular carcinoma risk. Thus, it does not specifically discuss recall bias in coffee consumption. Although dietary intake obtained by food frequency questionnaire is subject to misclassification, validation studies in subsamples of the included studies indicated that the consumption of coffee and other caffeine-containing beverages is assessed with good accuracy (Montella et al. 2007).
3) This comment refers to nondifferential misclassification of the disease, due to the use of cause of death listed on the death certificate. To address this, the study

[489] Jenab M, Boffetta P (2010). Glycemic index and glycemic load: application in observational studies and association with hepatocellular carcinoma risk. Meaningful or error prone? *Ann. Oncol.* 21(3):437-439.
[490] Shimazu et al. (2005), full citation provided in footnote 154.
[491] Sang LX, Chang B, Li XH, Jiang M (2013). Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. *BMC Gastroenterol*, 13(1):34.
[492] Greenland S, Lash TL (2008). Bias analysis, Chapter 19. In: Rothman KJ, Greenland S, Lash TL editors. *Modern Epidemiology* (3rd Edition). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, pp. 345-380.

by Shimazu et al. (2005) carried out an additional analysis that did not include the death certificate only cases. The inverse association between coffee consumption and the risk of primary liver cancer was not materially changed compared to the cases that were confirmed by medical records, and the authors think it is "unlikely that the DCO [death certificate only] cases distorted that inverse association substantially"[493].

4) This comment, which cites to Sang et al. (2013)[494], is referring to the possibility of misclassification bias occurring when all studies do not use the same form of measurement. While this is possible, it is important to note that significant inverse associations were observed in studies that compared ever coffee consumption to never coffee consumption. Thus, even if different units of measurement were used between studies, a protective effect was observed regardless of the amount consumed.

No changes to the proposed regulation were made based on this comment.

Comment 56 (CERT[495]): "[A]ccording to IARC, to find *evidence suggesting lack of carcinogenicity,* 'bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up.' However, nowhere in its discussion regarding coffee and liver cancer does IARC indicate whether the Working Group was able to rule out bias and confounding with reasonable confidence… Thus, OEHHA needs to resolve the impact of bias and confounding on reported liver cancer risk before accepting observations of inverse associations as being causally related to the consumption of coffee."

Epidemiological studies and meta-analyses of epidemiological studies have reported that, in addition to coffee, several other factors significantly reduce the risk of liver cancer: health dietary patterns, dietary fiber, vegetables, fish, tea, ginseng, other dietary factors, trace elements and vitamins, medications, hormone replacement therapy, reproductive factors (late age at menarche), and unknown factors.

Response 56: There is no evidence that IARC did not follow the guidance laid out in its Preamble[496] for ruling out confounding, bias, and reverse causation, with reasonable confidence. See also Responses to Comments 16, 17, 18 and 21. IARC examined

[493] Shimazu et al. (2005), full citation provided in footnote 154.
[494] Sang et al. (2013), full citation provided in footnote 491.
[495] CERT 18, pp. 104-109, 112-121, 172-174
[496] IARC (2018), full citation provided in footnote 3, pp. 9-32.

each study reviewed in the Monograph in terms of its ability to adequately adjust for potential confounders[497]. None of the factors listed by the commenter has been recognized as a known protective factor for liver cancer. For example, the only interventions established by the National Cancer Institute as having adequate evidence of decreased risk of hepatocellular carcinoma are HBV vaccination, treatment for chronic HBV infection, and availability of food not contaminated with aflatoxin B1[498].

Comprehensive reviews by other authoritative expert panels that have also addressed the issues of bias and confounding have made findings consistent with IARC's finding of an inverse association of risk for liver cancer with drinking coffee.

- As noted in the response to Comment 18, the Continuous Update Project expert panel[499] found that "There is strong evidence that coffee … REDUCES the risk of liver cancer."
- The US Food and Drug Administration's 2015 Dietary Guidelines Advisory Committee[500] concluded, based on its systematic review of the literature, that

> "consistent observational evidence indicates that regular consumption of coffee is associated with reduced risk of cancer of the liver and endometrium, and slightly inverse or null associations are observed for other cancer sites."

It is also noteworthy that in controlled animal studies coffee has exhibited effects protective of liver cancer. Male mice given coffee long term demonstrated significant reductions in liver adenomas, which can be precursor lesions to liver carcinomas[501]. In all three publications[502] reporting on studies of the co-carcinogenicity of brewed coffee and rodent liver carcinogens, coffee reduced the incidence or multiplicity of liver tumors. These findings further support the conclusion that liver cancer risk in humans is reduced by drinking coffee.

[497] IARC (2018), full citation provided in footnote 3, p. 61.
[498] NCI (2018), full citation provided in footnote 473.
[499] WCRF-AICR (2018), full citation provided in footnote 69.
[500] DGAC (2015), full citation provided in footnote 68.
[501] IARC (2018), full citation provided in footnote 3, pp. 339, 420.
[502] Silva-Oliveira EM, Fernandes PA, Moraes-Santos T (2010). Effect of coffee on chemical hepatocarcinogenesis in rats. *Nutr Cancer* 62(3):336–42; Nishikawa A, Tanaka T, Mori H (1986). An inhibitory effect of coffee on nitrosamine-hepatocarcinogenesis with aminopyrine and sodium nitrite in rats. *J Nutr Growth Cancer* 3:161–6; Furtado KS, Polletini J, Dias MC, Rodrigues MA, Barbisan LF (2014). Prevention of rat liver fibrosis and carcinogenesis by coffee and caffeine. *Food Chem Toxicol* 64:20–6.

No changes to the proposed regulation were made based on this comment.

Comment 57 (NCA[503]): NCA referenced two prospective studies by Park et al. (2018)[504] and Gapstur et al. (2017)[505] published after IARC completed its review. NCA also referenced four meta-analyses[506,507,508,509], two reviews[510,511], and one meeting abstract for an *in vitro* study[512].

Response 57: Regarding the prospective cohort studies referenced by NCA:

- Park et al. (2018)[513] was a prospective cohort study of 167,720 participants in the Multiethnic Cohort Study in Hawaii and Los Angeles. Coffee intake was inversely associated with liver cancer (HR = 0.57, 95% CI: 0.38–0.87, *p* trend <0.001).

- Gapstur et al. (2017)[514], was a prospective cohort mortality study that followed 922,896 Cancer Prevention Study-II participants from 1982 through 2012. Among non-smokers, coffee consumption was inversely associated with death from liver cancer (HR = 0.92, 95% CI: 0.88–0.96).

Regarding the meta-analyses cited by NCA that were released after the IARC 2016 meeting:

- Godos et al. (2017)[515] evaluated the association between coffee intake and biliary tract cancer and liver cancer risk. All studies addressing liver cancer risk were reviewed by IARC. The authors reported: “there was evidence of inverse correlation between coffee consumption and liver cancer risk. The association

[503] NCA, pp. 38-41
[504] Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW (2018). Prospective study of coffee consumption and cancer incidence in non-white populations. *Cancer Epidemiol. Biomarkers Prev*. 27(8):928-935.
[505] Gapstur et al. (2017), full citation provided in footnote 148.
[506] Godos J, Micek A, Marranzano M, Salomone F, Rio DD, Ray S (2017). Coffee consumption and risk of biliary tract cancers and liver cancer: a dose-response meta-analysis of prospective cohort studies. *Nutrients* 9(9):E950.
[507] Jarosz et al. (2017), full citation provided in footnote 341.
[508] Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J (2017). Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. *BMJ Open* 7(5):e013739.
[509] Bai K, Cai Q, Jiang Y, Lv L (2016). Coffee consumption and risk of hepatocellular carcinoma: a meta-analysis of eleven epidemiological studies. *Onco Targets Ther.* 9:4369-75.
[510] Heath RD, Brahmbhatt M, Tahan AC, Ibdah JA, Tahan V (2017). Coffee: The magical bean for liver diseases. *World J. Hepatol*. 9(15):689-696.
[511] Peacock A, Mattick RP, Bruno R (2017). A review of caffeine use as a risk or protective factor for women's health and pregnancy. *Curr. Opin. Psychiatry* 30(4):253-259.
[512] Wiltberger G, Lange U, Hau H, Seehofer D, Krenzien F, Benzing C et al. (2018). Protective effects of coffee consumption following liver transplantation for hepatocellular carcinoma. *Zeitschrift fur Gastroenterologie* 56(1).
[513] Park et al. (2018), full citation provided in footnote 504.
[514] Gapstur et al. (2017), full citation provided in footnote 148.
[515] Godos et al. (2017), full citation provided in footnote 506.

was consistent throughout the various potential confounding factors explored including smoking status, hepatitis, etc. Increasing coffee consumption by one cup per day was associated with a 15% reduction in liver cancer risk (RR 0.85; 95% CI 0.82 to 0.88)."

- Jarosz et al. (2017)[516] was a poster that did not contain sufficient information to evaluate the study. We also note that as a meeting abstract the study would not meet the IARC requirement for full consideration and summarization[517].
- Kennedy et al. (2017)[518] investigated coffee consumption and the risk of hepatocellular carcinoma. All studies in this meta-analysis were evaluated in IARC (2018) except one[519], an abstract from a poster that was not published in the peer-reviewed literature. The authors stated "We found 18 cohorts, involving 2 272 642 participants and 2905 cases, and 8 case-control studies, involving 1825 cases and 4652 controls. An extra two cups per day of coffee was associated with a 35% reduction in the risk of HCC [hepatocellular carcinoma]…The inverse association was weaker for cohorts (RR 0.71, 95% CI 0.65 to 0.77), which were generally of higher quality than case-control studies... There was evidence that the association was not significantly altered by stage of liver disease or the presence/absence of high alcohol consumption, high body mass index, type 2 diabetes mellitus, smoking, or hepatitis B and C viruses."
- Bai et al. (2016)[520] included 11 studies, all of which were evaluated in IARC (2018), and found an inverse association between coffee consumption and hepatocellular carcinoma risk.

IARC (2018) "concluded that a consistent, statistically significant, inverse association between coffee drinking and risk of liver cancer has been observed in multiple studies"[521]. The final evaluation stated, "There is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancers of the…liver", and that "Inverse associations with drinking coffee have been observed with cancers of the liver"[522]. The studies published after the IARC reviews referenced in the NCA submission that contain epidemiological data on liver cancer and coffee are consistent with this evaluation.

No changes to the proposed regulation were made based on this comment.

[516] Jarosz et al. (2017), full citation provided in footnote 341.
[517] IARC (2018), full citation provided in footnote 3, p. 12.
[518] Kennedy et al. (2017), full citation provided in footnote 508.
[519] Stucker I, N'Kontchou G, Loriot MA et al. (2006). Does coffee drinking protect cirrhotic patients against hepatocellular carcinoma? *Hepatology* 44:501A–01A.
[520] Bai et al. (2016), full citation provided in footnote 509.
[521] IARC (2018), full citation provided in footnote 3, p. 417.
[522] IARC (2018), full citation provided in footnote 3, p. 425.

Lung cancer

Comment 58 (CERT; NCA[523]): NCA referenced one prospective cohort study by Narita et al. (2018)[524] and one case-control study by Pasquet et al. (2016)[525] released after the IARC Monograph review, and noted that "neither study found an association between coffee consumption and an increased risk of lung cancer". CERT briefly discussed in the section of its comments "Coffee consumption increases the risk of several cancers" six meta-analyses, one of which was released after the Monograph meeting – Wang et al. 2016[526] – and another that was not included in the Monograph – Yu et al. (2011)[527]. The other four meta-analyses were discussed in the Monograph and considered by IARC in its evaluation. CERT also briefly describes one prospective cohort study released after the IARC Monograph meeting by Narita et al. (2018).

Response 58: Narita et al. (2018)[528], referenced by NCA and CERT, was a prospective cohort study in Japan that investigated the association between coffee drinking and incidence of lung cancer among 87,079 men and women with a mean follow-up of 17 years. Coffee consumption overall was not associated with risk of lung cancer in multivariable-adjusted models. When divided by type of lung cancer, coffee was associated with an increased risk of small cell carcinoma. A weakness of the study is that smoking was assessed only at baseline; 17 years of information on smoking status are missing. The observed association could be due to residual confounding by lifetime tobacco use, imperfect adjustment by lifetime tobacco use, or other risk factors. This study did not separately analyze never smokers.

Pasquet et al. (2016)[529], referenced by NCA, was a population-based case-control study in Montreal, Canada. The analyses included 1,130 cases and 1,483 controls. After adjusting for smoking status, coffee consumption was not associated with lung cancer risk.

Regarding the meta-analyses provided by CERT:

- Yu et al. (2011)[530] was did not find an association of coffee consumption with lung cancer. It included five cohort studies, all of which were included in IARC

[523] CERT 18, pp. 68-69, 87-89; NCA, pp. 41-42
[524] Narita S, Saito E, Sawada N, Shimazu T, Yamaji T, Iwasaki M et al. (2018). Coffee Consumption and Lung Cancer Risk: The Japan Public Health Center-Based Prospective Study. *J. Epidemiol.* 28(4);207-213.
[525] Pasquet R, Karp I, Siemiatycki J, Koushik A (2016). The consumption of coffee and black tea and the risk of lung cancer. *Annals of Epidemiology* 26:757-63.
[526] Wang et al. (2016), full citation provided in footnote 206.
[527] Yu et al. (2011), full citation provided in footnote 204.
[528] Narita et al. (2018), full citation provided in footnote 524.
[529] Pasquet et al. (2016), full citation provided in footnote 525.
[530] Yu et al. (2011), full citation provided in footnote 204.

(2018) except one. This study by Takezaki et al. (2003)[531] was a prospective cohort study that did not find an association of coffee consumption with lung cancer risk.

- Wang et al. (2016)[532], provided by CERT, was a meta-analysis of four prospective cohort studies on lung cancer. Coffee consumption was associated with an increased risk of lung cancer (summary RR = 2.18, 95% CI: 1.26–3.75). However, two of the studies in this meta-analysis did not adjust for smoking. These four studies were also reviewed by IARC (2018) and included in a different meta-analysis[533] reviewed by IARC that did not find an association of coffee drinking with lung cancer risk among nonsmokers (summary RR = 0.92, 95% CI: 0.75–1.10), suggesting there was residual confounding from smoking in Wang et al. (2016).

The summary of IARC (2018) stated, "In the most recent meta-analysis, coffee drinking was not associated with lung cancer when smoking was controlled. Among non-smokers, cohort, case–control studies and a meta-analysis did not find an association between coffee drinking and lung cancer. The Working Group concluded that the positive association between coffee drinking and lung cancer observed in some studies was probably explained by residual confounding due to smoking"[534]. Given the limitations of these additional studies, OEHHA finds there is not sufficient evidence to reach a different conclusion.

No changes to the proposed regulation were made based on this comment.

Oral cavity cancer

Comment 59 (NCA[535]): NCA referenced two meta-analyses published subsequent to the review by IARC (2018), Miranda et al. (2017)[536] and Li et al. (2016)[537].

[531] Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, Ohashi Y et al. (2003). Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. *Nutrition and Cancer* 45:160-67.
[532] Wang et al. (2016), full citation provided in footnote 206.
[533] Galarraga V, Boffetta P (2016). Coffee drinking and risk of lung cancer – a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* 25(6):951-957.
[534] IARC (2018), full citation provided in footnote 3, p. 418.
[535] NCA, pp. 42-43
[536] Wang et al. (2016), full citation provided in footnote 206.
[537] Li YM, Peng J, Li LZ (2016). Coffee consumption associated with reduced risk of oral cancer: a meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016 Apr;121(4):381-389.e1.

Response 59: Miranda et al. (2017)[538] was a meta-analysis of four cohort and 13 case-control studies that found an inverse association between coffee consumption and risk of oral and pharyngeal cancers. All studies were evaluated in IARC (2018) with the exception of one. This study, Hsu et al. (2012)[539], was a population-based case-control study conducted in Taiwan with 371 cases of nasopharyngeal carcinoma and 321 controls. Coffee consumption was associated with a decreased risk of nasopharyngeal carcinoma (OR = 0.56, 95% CI: 0.37–0.85) in this case-control study.

Li et al. (2016)[540] evaluated 11 case-control studies and four cohort studies of oral cancer and found odds ratios for case-control studies of 0.60 (95% CI: 0.49–0.74) and for cohort studies 0.66 (95% CI: 0.45–0.98). They concluded: "Overall, our results suggested that coffee consumption appears to have a protective benefit in oral cancer."

IARC (2018) stated, "Although data from several studies that combined results for the oral cavity and pharynx were suggestive of inverse associations, the Working Group concluded that these tumours are distinct entities and that the available data do not permit conclusions to be drawn about either cancer site"[541]. OEHHA finds that these additional meta-analyses do not provide sufficient evidence to draw conclusions beyond the evaluation made by IARC (2018).

No changes to the proposed regulation were made based on this comment.

Ovarian cancer

Comment 60 (Smith; CERT; NCA[542]): CERT in the section entitled "Coffee consumption increases the risk of several cancers" discussed four meta-analyses, two of which were considered by IARC, and two – Wang et al. (2016)[543] and Berretta et al. (2018)[544] – that were released after the IARC review.

[538] Miranda J, Monteiro L, Albuquerque R, Pacheco JJ, Khan Z, Lopez-Lopez J, Warnakulasuryia S (2017). Coffee is protective against oral and pharyngeal cancer: a systematic review and meta-analysis. *Med. Oral. Patol. Oral. Cir. Bucal.* 22(5):e554-e561.
[539] Hsu WL, Pan WH, Chien YC, Yu KJ, Cheng YJ, Chen JY et al. (2012). Lowered risk of nasopharyngeal carcinoma and intake of plant vitamin, fresh fish, green tea and coffee: a case-control study in Taiwan. *PLoS One* 7:e41779.
[540] Li et al. (2016), full citation provided in footnote 537.
[541] IARC (2018), full citation provided in footnote 3, p. 419.
[542] Smith, p. 3; CERT 18, pp. 50-51, 71-72; NCA, pp. 48-51
[543] Wang et al. (2016), full citation provided in footnote 206.
[544] Berretta M, Micek A, Lafranconi A, Rossetti S, Di Francia R, De Paoli P et al. (2018). Coffee consumption is not associated with ovarian cancer risk: a dose-response meta-analysis of prospective cohort studies. *Oncotarget* 9(29):20807-20815.

NCA introduced two prospective cohort studies (Park et al. 2018[545] and Arthur et al. 2018[546]), one case-control study (Leung et al. 2016[547]), one Mendelian randomization study (Ong et al. 2018), and two meta-analyses (Berretta et al. 2018[548] and Bamia et al. 2017[549]) that were released after IARC met in 2016. CERT also briefly described results from a meta-analysis from Steevens et al. (2007)[550].

Martyn Smith, NCA and CERT discussed a Mendelian randomization study of coffee and ovarian cancer – Ong et al. (2018)[551] – that was not available at the time of the IARC meeting in 2016. Dr. Smith and CERT indicated that since the study did not indicate inverse associations reported in observational studies of coffee, the findings (for coffee and ovarian cancer) are most likely due to confounding and reverse causation.

Response 60: Regarding the meta-analyses,

- Berretta et al. (2018)[552] analyzed eight prospective studies, all of which were considered by IARC. "We found no evidence of association between coffee consumption and ovarian cancer risk in both analysis on total group of women … and when considering only postmenopausal individuals."
- Wang et al. (2016)[553] included nine cohort studies, all of which were reviewed in IARC (2018). The study did not find an association of coffee drinking with ovarian cancer, and the authors reported: "The subgroup analysis indicated that there was no significant association between coffee intake and ovarian cancer risk in each subgroup."
- Bamia et al. (2017) was a meeting abstract for a presentation at a meeting that does not contain sufficient information for evaluation of the study quality.
- Steevens et al. (2007) reported, with few details, a meta-analysis that found a slight increase in ovarian cancer risk that was not statistically significant, while noting significant heterogeneity across the studies, indicative of study inconsistencies.

Regarding the observational studies referenced by NCA:

[545] Park et al. (2018), full citation provided in footnote 504.
[546] Arthur et al. (2018), full citation provided in footnote 245.
[547] Leung ACY, Cook LS, Swenerton K, Gilks B, Gallagher RP, Magliocco A et al. (2016). Tea, coffee, and caffeinated beverage consumption and risk of epithelial ovarian cancers. *Cancer Epidemiol.* 45:119-125.
[548] Berretta et al. (2018), full citation provided in footnote 544.
[549] Bamia et al. (2017), full citation provided in footnote 250.
[550] Steevens J, Schouten LJ, Verhage BAJ, Goldbohm RA, van den Brandt PA (2007). Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. *Br. J. Cancer* 97(9):1291-1294.
[551] Ong et al. (2018), full citation provided in footnote 80.
[552] Berretta et al. (2018), full citation provided in footnote 544.
[553] Wang et al. (2016), full citation provided in footnote 206.

- Leung at al. (2016), the population-based case-control study[554] referenced by NCA, was conducted in Alberta and British Columbia, Canada with 524 cases and 1,587 controls. Coffee consumption was not associated with epithelial ovarian cancer risk.
- Park et al. (2018) is a prospective cohort study[555] that evaluated the association between coffee consumption with overall cancer incidence and specific cancer sites in a large prospective study of 167,720 African Americans, Native Hawaiians, Japanese Americans, Latinos and whites in the US Multiethnic Cohort (MEC) of Hawaii and Los Angeles assembled in 1993–1996. Coffee intake was inversely associated with ovarian cancer (HR = 0.33, 95% CI: 0.17–0.65, *p* trend: 0.007).
- Arthur et al. (2018)[556] was a prospective cohort study that investigated the association between coffee intake and risk of ovarian cancer in Canadian women with a median 12.2-year follow-up. The study employed a case-cohort design: "A subcohort comprising 3185 women was created by randomly selecting an age stratified sample of participants from the total cohort at baseline (N=39,618 females)." This study found no association between coffee intake (either total coffee, caffeinated coffee, or decaffeinated coffee) for any level of exposure and the risk of ovarian cancer.

Ong et al. (2018)[557], referenced by Smith, NCA, and CERT, used genetic variants associated with coffee, tea, and/or caffeine consumption as proxies for exposure. The single nucleotide polymorphisms (SNPs) chosen were associated with the aryl hydrocarbon receptor (*AHR*) and cytochrome P450 1A1/2 (*CYP1A1*/*CYP1A2*) genes because both are known to play a functional role in caffeine metabolism[558]. While Mendelian randomization studies can be advantageous in that they may reduce the impact of confounding, these studies used genetic variants as proxies for coffee drinking and are not specific to coffee, as these variants can also be associated with consumption of other caffeinated beverages such as tea. Further considerations regarding the validity of these studies for particular applications are discussed in the response to Comment 20. In the Ong et al. study, the causal odds ratio for the association between the proxy genes for coffee and all ovarian cancer was 0.92 (with 95% confidence interval of 0.79–1.06). Thus, no association was seen with coffee and ovarian cancer in this study.

[554] Leung et al. (2016), full citation provided in footnote 547.
[555] Park et al. (2018), full citation provided in footnote 504.
[556] Arthur et al. (2018), full citation provided in footnote 245.
[557] Ong et al. (2018), full citation provided in footnote 80.
[558] Cornelis MC, Monda KL, Yu K, Paynter N, Azzato EM, Bennett SN (2011). Genome-wide meta-analysis identifies regions on 7q21 (*AHR*) and 15q24 (*CYP1A2*) as determinants of habitual caffeine consumption. *PLoS Genet* 7(4): e1002033. doi:10.1371/journal.pgen.1002033.

The IARC (2018) summary states, “Evidence from the majority of the cohort studies, including the largest one and a meta-analysis, suggests no association. The evidence from case–control studies is inconsistent; although the majority of studies suggest a null association, some others show (mostly non-statistically significant) positive associations. Given the inconsistency of the results among studies, the Working Group found the evidence to be inconclusive.” OEHHA finds that the results of the more recent studies show either no association or inverse associations. They do not show elevated risk.

No changes to the regulation were made based on this comment.

Pancreatic Cancer

Comment 61 (CERT; NCA[559]): CERT briefly describes results for six meta-analyses, two of which were released after the Monograph meeting, Wang et al. (2016)[560] and Nie et al. (2016)[561]. The CERT presentation of these studies was in the section “Coffee consumption increases the risk of several cancers.” (V.B). NCA referenced one mortality study[562] released after the IARC Monograph meeting that had information on pancreatic cancer.

Response 61: Regarding the meta-analyses discussed by CERT:

- Wang et al. (2016) conducted meta-analyses of cohort studies to investigate the association between coffee and many cancer types. The meta-analysis, based on 15 cohort studies (all of which were evaluated in IARC 2018), did not find an association between coffee consumption and pancreatic cancer.
- Nie et al. (2016), mentioned by CERT, was a meta-analysis[563] of 20 prospective cohort studies, all of which were evaluated in IARC (2018). There was no association between coffee consumption and pancreatic cancer in the highest intake compared to the lowest category in the summary relative risks and in subgroup analyses. The authors reported that dose-response analysis (based on data from 10 studies) indicated that every one-cup increase in coffee consumption was associated with a 1% increase in pancreatic cancer risk.

[559] CERT 18, pp. 73-74; NCA, pp. 17-21
[560] Wang et al. (2016), full citation provided in footnote 206.
[561] Nie K, Zing Z, Huang W, Wang W, Liu W (2016). Coffee intake and risk of pancreatic cancer: an updated meta-analysis of prospective studies. *Minerva Med.* 107(4):270-278.
[562] Loftfield et al. (2018), full citation provided in footnote 252.
[563] Nie et al. (2016), full citation provided in footnote 561.

However, no *p* values were reported, and there were not enough details for OEHHA to evaluate this statement.

- The four remaining meta-analyses were adequately considered in the IARC Monograph.

Regarding the paper referenced by NCA, Loftfield et al. (2018)[564] is discussed in the multicancer section of the NCA comments. It was a prospective cohort study that evaluated associations of coffee drinking with all-cause and cause-specific mortality in the UK Biobank. Coffee consumption was not associated with increased risk of death from pancreatic cancer in multivariable-adjusted models.

IARC found "[t]here is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancers of the pancreas"[565]. OEHHA finds that the three studies provided by the commenters do not provide evidence indicating that IARC's evaluation should be updated.

No changes to the proposed regulation were made based on this comment.

Comment 62 (CERT[566]): In its evaluation of pancreatic cancer, "IARC does not discuss whether the null association it observed for consumption of coffee and pancreatic cancer may be influenced by confounding due to factors that have been reported to reduce the risk of pancreatic cancer. In fact, many factors have been reported in meta-analyses to significantly reduce risk of pancreatic cancer."

Response 62: There is no evidence that IARC did not follow the guidance laid out in its Preamble[567] for ruling out confounding, bias, and reverse causation with reasonable confidence. See also Responses to Comments 16, 17, 18, 21.

No changes to the proposed regulation were made based on this comment.

Prostate cancer

Comment 63 (CERT; NCA; Smith[568]): IARC found evidence of lack of carcinogenicity for prostate cancer, however it does not appear that IARC considered "confounding of the association between coffee and prostate cancer by the numerous factors that have

[564] *Ibid*.
[565] IARC (2018), full citation provided in footnote 3, p. 425.
[566] CERT 18, pp. 178-188
[567] IARC (2018), full citation provided in footnote 3, pp. 16-20.
[568] CERT 18, pp. 188-205; NCA, p. 45; Smith, pp. 3-4.

been reported to decrease the risk of prostate cancer in meta-analyses of observational studies".

The commenters discussed various factors such as medications, physical activity, medical conditions, dietary factors and vitamins. They referred to a Mendelian randomization study by Taylor et al. (2017) [569] published after the IARC review as "the most important study regarding coffee consumption and prostate cancer".

"A Mendelian randomization study of genetically predicted coffee consumption did not confirm the inverse association, but instead reported a small, but significantly increased risk of nonlocalized prostate cancer compared to localized stage disease (OR = 1.03, 95% CI: 1.01–1.06)" (Smith, p. 4).

NCA discussed the same study, noting, "There were many limitations inherent to the study protocol, including [quoting from the study author] "statistical power to detect associations in Mendelian randomization studies is substantially lower than conventional observational analyses."

Response 63: In its review of the epidemiology studies of coffee consumption and risk of prostate cancer, IARC took into consideration possible sources of confounding, and placed greater weight on studies that appropriately adjusted for confounding factors. IARC indicated limitations of studies that did not adjust for particular risk factors. For each study evaluated, IARC noted the covariates for which the studies controlled. IARC also placed "the greatest weight on aggressive and fatal cancers to reduce the potential for bias from screening."

Contrary to CERT's and Smith's statements that the study on Mendelian randomization by Taylor et al. (2017)[570] contradicted IARC's conclusions on prostate cancer, the study authors noted:

> "Amongst men with prostate cancer, there was no clear association between the genetic risk score and all-cause mortality (HR: 1.00, 95% CI: 0.97, 1.04) or prostate cancer-specific mortality (HR: 1.03, 95% CI: 0.98, 1.08). These results, which should have less bias from confounding than observational estimates, are not consistent with a substantial effect of coffee consumption on reducing prostate cancer incidence or progression."

Taylor et al. also noted:

[569] Taylor et al. (2017), full citation provided in footnote 79.
[570] *Ibid*.

> "Although point estimates are very close to the null for most findings, we cannot rule out the possibility that coffee may have small effects on prostate cancer. For example, the meta‐analysis of coffee and prostate cancer conducted by Lu and colleagues in 2014 reports an OR of 0.96 for prostate cancer risk for the highest (at least ⩾4 cups per day) compared to the lowest categories of consumption (generally < 1 cup per day),"

thus pointing out the possibility of a small potential decreased risk.

Using Mendelian randomization as an approach to fully address confounding issues for coffee can be problematic, as noted in the response to Comment 20.

Regarding the extent to which IARC considered confounding, an important confounder in studies of prostate cancer mortality and coffee is cigarette smoking. The IARC Monograph stated:

> "Smoking … is associated with prostate cancer mortality (US Department of Health and Human Services, 2014). Because smoking is also strongly associated with coffee intake in many populations, and because many high-quality studies of coffee and prostate cancer with adjustment for smoking are available, those without adjustment for smoking were excluded."[571]

No changes to the proposed regulation were made based on this comment.

Comment 64 (Smith, CERT 18, NCA[572]): In a section entitled "Coffee consumption increases the risk of several cancers" CERT discusses ten meta-analyses studies, two of which were released after the IARC meeting – Wang et al. (2016)[573], Xia et al. (2017)[574]; and an additional meta-analysis that was not considered by IARC[575].

In a section entitled "IARC's evaluation of cancer risks associated with coffee" CERT states "Epidemiologic studies regarding consumption of coffee and prostate cancer report inconsistent results…" CERT also in that section:

- provides references for: 14 case-control studies, stating that most provided increased risks. In CERT's very brief descriptions of results, four showed

[571] IARC (2018), full citation provided in footnote 3, p. 258
[572] Smith, pp. 4-5; CERT 18, pp. 41-52, 74-76, 89-90, 188-205; NCA, pp. 43-46
[573] Wang et al. (2016), full citation provided in footnote 206.
[574] Xia J-D, Chen J, Xue J-X, Yang J, Wang Z-J (2017). An up-to-date meta-analysis of coffee consumption and risk of prostate cancer. *Urology J.* 14(5):4079-4088.
[575] Huang et al. (2014), full citation provided in footnote 205.

significant results. CERT then provided a one sentence synopsis of a recent case-control study[576] released after the IARC Monograph meeting. All but one[577] of the studies provided that were released before the IARC meeting were reviewed in the Monograph;

- indicates 15 cohort studies have been reported, and CERT contends that they show increased and decreased risk of prostate cancer, referencing "Report of Dr. Peter Infante for the Phase 2 trial in the *CERT v. Starbucks* case", and highlighting "EPIC cohort, which reported risks slightly above unity for three consumption categories"; and
- provides 10 meta-analyses described earlier in the section "Coffee consumption increases the risk of several cancers" (V.B.10).

NCA states "Since the IARC evaluation, there have been seven studies looking at the relationship between coffee consumption and prostate cancer. All but one of the studies found evidence that coffee consumption was associated with a decreased risk of prostate cancer". The commenter tabulates and provides brief comments on

- two prospective cohort studies: Sen et al. (2019)[578], Pounis et al. (2017)[579];
- one case-control study: Russo et al. (2017)[580];
- one meta-analysis: Xia et al. (2017)[581];
- the Taylor et al. (2017) Mendelian randomization paper discussed in Comment 20 above; and
- two review papers: Grosso et al. (2017)[582], Peisch et al. (2017)[583].

Response 64: CERT's statement "Epidemiologic studies regarding consumption of coffee and prostate cancer report inconsistent results," is incorrect. IARC summarized the evidence as follows[584]:

[576] Russnes KM, Möller E, Wilson KM, Carlsen M, Blomhoff R, Smeland S et al. (2016). Total antioxidant intake and prostate cancer in the Cancer of the Prostate in Sweden (CAPS) study. A case control study. *BMC Cancer* 16:438.
[577] De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Acosta G (2011). Alcohol drinking, non-alcoholic beverages and risk of advanced prostate cancer among Uruguayan men. *J. Cancer Sci. Ther.* S1:006.
[578] Sen A, Papadimitriou N, Lagiou P, Perez-Cornago A, Travis RC, Key TJ et al. (2019). Coffee and tea consumption and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *Int. J. Cancer* 144(2):240-250. [OEHHA notes that the comment cited Sen et al. (2018), which was the earlier version pre-published online]
[579] Pounis G, Tabolacci C, Costanzo S, Cordella M, Bonaccio M, Rago L et al. (2017). Reduction by coffee consumption of prostate cancer risk: Evidence from the Moli-sani cohort and cellular models. *Int J Cancer* 141:72-82.
[580] Russo GI, Campisi D, Di Mauro M, Regis F, Reale G, Marranzano M et al. (2017). Dietary consumption of phenolic acids and prostate cancer: a case-control study in Sicily, southern Italy. *Molecules* 22:E2159.
[581] Xia et al. (2017), full citation provided in footnote 574.
[582] Grosso et al. (2017), full citation provided in footnote 251.
[583] Peisch SF, Van Blarigan EL, Chan JM, Stampfer MJ, Kenfield SA (2017). Prostate cancer progression and mortality: a review of diet and lifestyle factors. *World J. Urol.* 35(6):867-874.
[584] IARC (2018), full citation provided in footnote 3, pp. 417-418.

> "Evidence from ten cohort studies and four case–control studies of the association between coffee drinking and cancer of the prostate was evaluated. The greatest weight was given to studies of aggressive and fatal prostate cancer to reduce the potential for bias from screening. No case–control or cohort studies found positive associations with the risk of total prostate cancer. Recent meta-analyses of cohort and case–control studies estimated inverse associations for fatal prostate cancer and no association for advanced prostate cancer. Studies conducted worldwide consistently indicated no increased risk of prostate cancer associated with coffee drinking, with inverse or null associations observed in all studies."

All of the studies released since the IARC meeting in 2016 have indicated either protective or no effects of coffee on prostate cancer.

Regarding the meta-analyses:

- Wang et al. (2016)[585], referenced by CERT, included 14 cohort studies and found either no association or a reduced association of coffee intake with prostate cancer. One of these studies[586] was not evaluated in IARC (2018). This study, by Allen et al. (2004), was a prospective study that did not find an association of coffee consumption with prostate cancer risk.
- Xia et al. (2017)[587], referenced by CERT and NCA, included studies that did not adjust for smoking into their combined meta- risk estimate and did not conduct further sensitivity analyses of studies that adjusted for smoking versus those that did not. This is problematic. As explained in IARC (2018), "Studies that did not control for smoking behaviour were judged to be non-informative. Smoking is not associated with total prostate cancer incidence, but is associated with prostate cancer mortality (US Department of Health and Human Services, 2014)."
- Huang et al. (2014)[588], mentioned by CERT, included studies that did and did not adjust for smoking. The summary analysis of only studies that adjusted for smoking found an inverse risk of prostate cancer with coffee consumption (summary RR = 0.90, 95% CI: 0.85 – 0.96).

Regarding the observational studies:

[585] Wang et al. (2016), full citation provided in footnote 206.
[586] Allen NE, Sauvaget C, Roddam AW, Appleby P, Nagano J, Suzuki G et al. (2004). A prospective study of diet and prostate cancer in Japanese men. *Cancer Causes & Control* 15: 911–920.
[587] Xia et al. (2017), full citation provided in footnote 574.
[588] Huang et al. (2014), full citation provided in footnote 205.

- Russnes et al. (2016)[589], referenced by CERT, was a population-based case-control study conducted in Sweden that found reduced risk of prostate cancer associated with coffee consumption.
- Taylor et al. (2017)[590], referenced by CERT and NCA, was the Mendelian randomization study that did not find an association with prostate cancer and cytochrome P450 1A1/2 (*CYP1A1*/*CYP1A2*) genes known to play a functional role in caffeine metabolism[591]. See Response to Comment 20.
- Russo et al. (2017)[592], referenced by NCA, assessed the association of dietary consumption of phenolic acids and prostate cancer. It did not analyze coffee drinking independently.
- Sen et al. (2019)[593], referenced by NCA, was a prospective cohort study that evaluated prostate cancer risk in 142,196 men from the European Prospective Investigation into Cancer and Nutrition with an average follow-up of 14 years. Coffee consumption was not associated with prostate cancer risk by cancer grade, stage, fatality, or according to age, BMI, smoking status, and physical activity.
- Pounis et al. (2017)[594] was a prospective cohort study of 6,989 men from the Moli-sani Project (Italy) followed for a mean of 4.24 years. Coffee consumption was associated with a reduced risk of prostate cancer.

Regarding the review papers referenced by NCA:

- Peisch et al. (2017) reviews lifestyle and dietary factors that may play a role in reducing prostate cancer progression, and concluded coffee may be beneficial. All studies included in the paper on the association of prostate cancer incidence and coffee consumptions were included in IARC (2018).
- Grosso et al. (2017) was a review paper that included an umbrella meta-analysis and concluded “coffee was associated with a probable decreased risk of … prostate cancer.”

De Stefani et al. (2011)[595], submitted by CERT but not included in the IARC Monograph, was a hospital-based case-control study conducted in Uruguay (345 cases; 1,296 controls). This study reported two unusual results that raise concerns regarding its quality.

[589] Russnes et al. (2016), full citation provided in footnote 576.
[590] Taylor et al. (2017), full citation provided in footnote 79.
[591] Cornelis et al. (2011), full citation provided in footnote 558.
[592] Russo et al. (2017), full citation provided in footnote 580.
[593] Sen et al. (2019), full citation provided in footnote 578.
[594] Pounis et al. (2017), full citation provided in footnote 579.
[595] De Stefani et al. (2011), full citation provided in footnote 577.

1) Smoking duration (analyzed as a continuous variable) had a protective effect on advanced prostate cancer. This is in contrast to the findings in the Surgeon General's report on Smoking and Health[596] where smoking was associated with prostate cancer progression and mortality.

2) An increased risk of advanced prostate cancer was observed for those who had the highest coffee intake (⩾ seven cups/week) compared with never drinkers. This was the only study to report a positive association between coffee drinking and prostate cancer.

These unusual findings reported for smoking and coffee could result from a bias in the selection of controls into this study. The authors stated that the controls selected had "non-neoplastic conditions not related to smoking, drinking, and without recent changes in their diets". If this were true, the proportion of smokers should be roughly equal in the case and control groups. However, there was a higher proportion of controls who smoked for 1-49 years compared to the case group (Table 1 of the publication). This would result in a risk estimate biased toward the null and underestimate the effect of smoking.

Furthermore, nearly a third of the controls, with diagnoses of urinary stones and abdominal hernia[597], may have decreased their coffee intake after onset of symptoms. This would result in a risk estimate biased away from the null and overestimate the effect of coffee.

IARC (2018) concluded:

> "There is *evidence suggesting lack of carcinogenicity* of drinking coffee in humans for cancers of the …prostate".

OEHHA finds that the state of the current data on prostate cancer remains consistent with that conclusion.

No changes to the proposed regulation were made based on this comment.

[596] US DHHS (2014), full citation provided in footnote 121. Chapter 6 Cancer, Prostate Cancer, pp. 204-209.
[597] IARC (2018) considered digestive and urologic disorders a limitation of hospital-based case-control studies. For example, "Hospital controls included patients with digestive system problems (16%), heart disease (17%), and hypertension diseases (12%), all of which could affect coffee drinking and lead to bias" (IARC 2018, p. 143).

Renal cell cancer

Comment 65 (NCA[598]): NCA briefly described one case-control study (Antwi et al. 2017)[599] and one meta-analysis (Wijampreecha et al. 2017)[600] that were released after the IARC review.

Response 65: Antwi et al. (2017)[601] was a hospital-based case-control study of 669 cases of renal cell carcinoma and 1,001 controls. This study found an inverse association between caffeinated coffee consumption and renal cell carcinoma risk (OR = 0.74, 95% CI: 0.57–0.99). The association was not statistically significant for decaffeinated coffee (OR = 1.47, 95% CI: 0.98–2.19).

Wijarnpreecha et al. (2017)[602] was a meta-analysis that included six cohort studies and 16 case-control studies that found no associations between coffee consumption and renal cell carcinoma risk in pooled analyses. Of these studies, six case-control studies were not reviewed in IARC (2018). McLaughlin et al. (1984)[603] was a population-based case-control study that found no association between coffee consumption and renal cell carcinoma in men or women. Asal et al. (1988)[604] was a case-control study that included both hospital- and population-based controls. Coffee drinking was associated with risk of renal cell carcinoma in women in the hospital-based control comparison (details of group numbers not provided). There was no information on the analysis in men. Mellemgaard et al. (1994)[605], Kreiger et al. (1993)[606], and Yuan et al. (1998)[607] are population-based case-control studies that found no significant associations of coffee drinking with risk of renal cell carcinoma. Wolk et al. (1996)[608] was a population-based case-control study that had 1,185 renal cell cancer cases and 1,526 controls. The authors adjusted for BMI, smoking, and total calories. This study found no association with renal cell cancer in men and a positive association in women for

[598] NCA, pp. 32-33
[599] Antwi SO, Eckel-Passow JE, Diehl ND, Serie DJ, Custer KM, Arnold ML et al. (2017). Coffee consumption and risk of renal cell carcinoma. *Cancer Causes Control* 28(8):857-866.
[600] Wijarnpreecha K, Thongprayoon C, Thamcharoen N, Panjawatanan P, Cheungpasitporn W (2017). Association between coffee consumption and risk of renal cell carcinoma: a meta-analysis. *Internal Medicine Journal* 47:1422–1432.
[601] Antwi et al. (2017), full citation provided in footnote 599.
[602] Wijarnpreecha et al. (2017), full citation provided in footnote 600.
[603] McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni JF (1984). A population-based case-control study of renal cell carcinoma. *JNCL* 72:275-84.
[604] Asal NR, Risser DR, Kadamani S, Geyer JR, Lee ET, Cherng N (1988). Risk factors in renal cell carcinoma: I. Methodology, demographics, tobacco, beverage use, and obesity. *Cancer Detect. & Prev.* 11:359-77.
[605] Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH (1994). Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. *Cancer Causes and Control* 5:105-113.
[606] Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA (1993). Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes and Control* 4:101-110.
[607] Yuan JM, Gago-Dominguez M, Castelao JE, Hankin JH, Ross RK, Yu MC (1998). Cruciferous vegetables in relation to renal cell carcinoma. *Int J Cancer* 77:211-216.
[608] Wolk et al. (1996), full citation provided in footnote 113.

consumption of 42 or greater cups of coffee per week. This difference in risk by sex has not been confirmed in other studies, and confounding may have contributed to the results. The authors did not adjust for hypertension or diabetes status, which are also risk factors for renal cell carcinoma[609], and could bias the results away from the null.

The IARC (2018) summary stated,

> "For renal cell carcinoma, four cohort studies (including a pooled analysis of prospective cohort studies) and five case–control studies were considered informative. The largest study pooled data from 13 prospective cohorts and found no overall association; statistically significant inverse associations among women and among never-smokers were observed, with comprehensive adjustment for confounders. One large, well-conducted population-based case–control study found a statistically significant positive association, and the remaining studies were either null or significantly inverse"[610].

Overall, IARC (2018) concluded that there was inadequate evidence of carcinogenicity. OEHHA finds that the additional studies released after the report are consistent with this conclusion.

No changes to the proposed regulation were made based on this comment.

Skin Cancer

Melanoma

Comment 66 (CERT; NCA[611]): CERT refers to five meta-analyses on coffee consumption and the risk of melanoma, all showing either null or protective effects. Of these meta-analyses,[612,613] two were released after the IARC 2016 meeting. CERT also discusses one prospective cohort study[614] on melanoma. CERT also discusses studies on melanoma and smoking, noting inverse dose response relationships. This is in the section entitled "OEHHA's claim that coffee is unique", in the subsection, "Coffee and smoking are associated with reduced risk of certain cancers" (XI.A.3).

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[609] "Type 2 diabetes, obesity, and hypertension are also risk factors for renal cell carcinoma; this risk is significant given coffee's consistent inverse association with type 2 diabetes risk, and its positive effects on insulin levels and glucose metabolism." IARC (2018), full citation provided in footnote 3, p. 304.
[610] IARC (2018), full citation provided in footnote 3, p. 419.
[611] CERT 18, pp. 300-303; NCA pp. 19, 46-48
[612] Micek A, Godos J, Lafranconi A, Marranzano M, Pajak A (2018). Caffeinated and decaffeinated coffee consumption and melanoma risk: a dose-response meta-analysis of prospective cohort studies. *Int J Food Sci and Nutr* 69:417-426.
[613] Wang et al. (2016), full citation provided in footnote 206.
[614] Park et al. (2018), full citation provided in footnote 504.

NCA referenced two studies[615,616], one meta-analysis[617], and two reviews[618,619] on skin cancer that were released after the 2016 meeting.

Response 66: First, regarding the matter of smoking, OEHHA notes in IARC's most recent Monograph on Tobacco Smoking, it did not find melanoma to be one of the many types of cancer caused by tobacco, but nor did IARC identify melanoma as a cancer type for which there was evidence suggesting lack of carcinogenicity for tobacco smoke. Nonetheless IARC did note:

> "The possibility that smoking may reduce the risk for melanoma should, therefore, be considered."[620]

Regarding the studies briefly noted by CERT and/or NCA:

- Park et al. (2018)[621] was a prospective cohort study that evaluated the association between coffee consumption with overall cancer incidence and specific cancer sites in a large population of 167,720 African Americans, Native Hawaiians, Japanese Americans, Latinos and whites in the US Multiethnic Cohort (MEC) of Hawaii and Los Angeles assembled in 1993–1996. Coffee intake was associated inversely with melanoma (HR = 0.72, 95% CI: 0.52–0.99, *p* trend: 0.002).

- Micek et al. (2018)[622] was a meta-analysis that identified seven prospective cohort studies. The authors found that an increase in coffee consumption of one cup per day was associated with a reduction in melanoma risk (RR = 0.97, 95% CI: 0.95–0.99). All studies except two were reviewed in IARC (2018). Caini et al. (2017a)[623] is discussed below. Lukic et al. (2016)[624] was a prospective cohort study that investigated the association between coffee consumption and malignant melanoma in 104,080 women in the Norwegian Women and Cancer Study. Coffee intake was inversely associated with melanoma risk in low-moderate consumers (>1-3 cups/day, HR = 0.80, 95% CI: 0.66–0.98) and in

[615] Caini S, Masala G, Saieva C, Kvaskoff M, Savoye I, Sacerdote C et al. (2017a). Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 140:2246-55.
[616] Park et al. (2018), full citation provided in footnote 504.
[617] Micek et al. (2018), full citation provided in footnote 612.
[618] Yang K, Fung T, Nan H. (2018). An epidemiological review of diet and cutaneous malignant melanoma. *Cancer Epidemiol. Biomarkers Prev.* 27:1115-22.
[619] Peacock et al. (2017), full citation provided in footnote 511.
[620] IARC (2012a), full citation provided in footnote 146, pp. 109 and 167, Available at: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100E-6.pdf
[621] Park et al. (2018), full citation provided in footnote 504.
[622] Micek et al. (2018), full citation provided in footnote 612.
[623] Caini et al. (2017a), full citation provided in footnote 615.
[624] Lukic et al. (2016), full citation provided in footnote 305.

high-moderate consumers (>3-5 cups/day, HR = 0.77, 95% CI: 0.61–0.97) compared to light consumers (⩽1 cup/day).

- Wang et al. (2016)[625] was a meta-analysis that included six cohort studies (all of which were reviewed in IARC (2018)), and found an inverse association of coffee consumption with melanoma risk (summary RR = 0.89, 95% CI: 0.80–0.99).

- Caini et al. (2017a)[626] was a prospective study that evaluated the relationship between coffee consumption and risk of melanoma in the EPIC cohort. A total of 476,160 participants were followed up for a mean of 14.9 years. Consumption of caffeinated coffee was inversely associated with melanoma risk among men for the highest quartile of consumption vs. non-consumers (HR = 0.31, 95% CI: 0.14–0.69) but not among women (HR = 0.96, 95% CI: 0.62–1.47). Yang et al. (2018)[627] was a review referenced by NCA. All studies in Yang et al. (2018) were reviewed in IARC (2018) with the exception of Caini et al. (2017a). Peacock et al. (2017)[628], another review referenced by NCA, cited two melanoma studies, and both studies were included in IARC (2018).

The IARC (2018) summary stated, “Thirteen studies – seven cohort studies and six case–control studies – reported inconsistent results for an association between coffee consumption and risk of cutaneous malignant melanoma.”[629] IARC then goes on to discuss studies mostly showing null or inverse associations. The additional studies reported either null or inverse associations. Taken together with the studies reviewed by IARC, these additional studies support IARC’s finding of “inadequate evidence of carcinogenicity” for malignant melanoma, while at the same time providing further evidence for null and inverse relationships.

No changes to the proposed regulation were made based on this comment.

[625] Wang et al. (2016), full citation provided in footnote 206.
[626] Caini et al. (2017a), full citation provided in footnote 615.
[627] Yang et al. (2018), full citation provided in footnote 618.
[628] Peacock et al. (2017), full citation provided in footnote 511.
[629] IARC (2018), full citation provided in footnote 3, p. 420.

Non-melanoma skin cancer.

Comment 67 (NCA[630]): NCA provided two meta-analyses[631,632] and one review[633] that were released after the IARC 2016 review.

Response 67: Caini et al. (2017b)[634] was based on seven studies, six of which were reviewed in IARC (2018). The one study that IARC did not review, Abel et al. (2007)[635], was a cross-sectional analysis of women enrolled in the Women's Health Initiative Observational Study. Coffee consumption was evaluated by a questionnaire that women completed at time of enrollment based on current consumption and consumption for the past 3 months. History of skin cancer was also ascertained by a self-reported questionnaire. This study found a reduced risk of non-melanoma skin cancer with coffee consumption; however, the limitations of the study design preclude it from being an informative study.

Vaseghi et al. (2016)[636] included six studies, four of which were reviewed in IARC (2018). The two studies not reviewed were Abel et al. (2007) and Husein-ElAhmed et al. (2013)[637]. The latter study investigated the association of nutrient intake with cutaneous solar elastosis adjacent to basal cell carcinoma. Coffee consumption was not associated with risk of basal cell carcinoma.

The IARC (2018) summary stated, "Three cohort studies and three case–control studies have reported on the association between coffee consumption and risk of non-melanoma skin cancer. All of the studies reported null or inverse associations with coffee drinking"[638]. These additional studies also reported either null or inverse associations.

No changes to the proposed regulation were made based on this comment.

[630] NCA, pp. 46-48
[631] Caini S, Cattaruzza S, Bendinelli B, Tosti G, Masala G, Gnagnarella P et al. (2017b). Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis. *Eur. J. Nutr.* 65:1-12.
[632] Vaseghi G, Haghjoo-Javanmard S, Naderi J, Eshraghi A, Mahdavi M, Mansourian M (2016). Coffee consumption and risk of nonmelanoma skin cancer: a dose-response meta-analysis. *Eur. J. Cancer Prev.* 27(2):164-170.
[633] Peacock et al. (2017), full citation provided in footnote 511.
[634] Caini et al. (2017b), full citation provided in footnote 631.
[635] Abel EL, Hendrix SO, McNeeley SG, Johnson KC, Rosenberg CA, Mossavar-Rahmani Y et al. (2007). Daily coffee consumption and prevalence of nonmelanoma skin cancer in Caucasian women. *Eur. J. Canc Prev* 16:446-52.
[636] Vaseghi et al. (2016), full citation provided in footnote 632.
[637] Husein-ElAhmed J, Aneiros-Fernandez MT, Gutierrez-Salmeron J, Aneiros-Cachaza R, Naranjo S (2013). Relationship between food intake and cutaneous solar elastosis adjacent to basal cell carcinoma. *J. Eur. Acad. Dermatol. Venereol.* 27:25–30.
[638] IARC (2018), full citation provided in footnote 3, p. 420.

Stomach cancer

Comment 68 (CERT[639]): CERT briefly describes the results of nine meta-analyses of stomach cancer under section (V) of its comments "Coffee consumption increases the risk of several cancers." Only one was not referenced by IARC, Xie et al. (2016)[640], which was released after the IARC 2016 review. CERT also briefly describes results from one cohort study by Lukic et al. (2018b)[641], also referenced by NCA.

Response 68: The prospective cohort study referenced by CERT and NCA, Lukic et al. (2018b)[642], used data from the Norwegian Women and Cancer Study and the Northern Sweden Health and Disease Study to examine cancer sites by category of total, filtered, and boiled coffee consumption. The study did not find evidence of an association between total coffee consumption and risk of stomach cancer in moderate or heavy total coffee consumers compared to light total coffee consumers and in sex-specific analyses. There was one positive finding in subgroup analyses of filtered vs. boiled coffee: Never smokers who drank four or more cups of boiled coffee per day were reported having a greater risk of stomach cancer compared to never smokers who drank one cup or less of boiled coffee per day (*p* trend: 0.04).

Xie et al. (2016)[643] was a meta-analysis that included 22 studies (nine cohort and 13 case-control studies), and found that coffee consumption was associated with decreased risks of gastric cancer. All but three studies[644,645,646] were included in IARC (2018). Ji et al. (1996)[647] did not have many cases (21/1,124) or controls (32/1,249) that reported drinking coffee, and it did not report ORs for coffee consumption. Memik et al. (1992)[648] was a case-control study that did not find any associations between coffee consumption and stomach cancer. Lee et al. (1990)[649] was a hospital-based case-control study that did not find a significant positive association of coffee consumption with stomach cancer.

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[639] CERT 18, pp. 63-65
[640] Xie Y, Huang S, He T, Su Y (2016). Coffee consumption and risk of gastric cancer: an updated meta-analysis. *Asia Pac. J. Clin. Nutr.* 25(3):578-588.
[641] Lukic et al. (2018b), full citation provided in footnote 198.
[642] *Ibid*.
[643] Xie et al. (2016), full citation provided in footnote 640.
[644] Ji B, Chow W, Yang G, McLaughlin J, Gao R, Zheng W et al. (1996). The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer* 77:2449-56.
[645] Memik F, Nak SG, Gulten M, Ozturk M (1992). Gastric carcinoma in northwestern Turkey: epidemiologic characteristics. *J. Environ. Pathol. Toxicol. Oncol.* 11:335-8.
[646] Lee HH, Wu HY, Chuang YC, Chang AS, Chao HH, Chen KY et al. (1990). Epidemiologic characteristics and multiple risk factors of stomach cancer in Taiwan. *Anticancer Res.* 10:875-81.
[647] Ji et al. (1996), full citation provided in footnote 644.
[648] Memik et al. (1992), full citation provided in footnote 645.
[649] Lee et al. (1990), full citation provided in footnote 646.

The summary of IARC (2018) stated that the studies "of the association between coffee drinking and gastric cancer reported inconsistent results, with no consistent evidence of a positive or inverse association between coffee intake and gastric cancer observed"[650]. OEHHA finds that these additional studies, which mostly show no effect, are consistent with this conclusion.

No changes to the proposed regulation were made based on this comment.

Thyroid cancer

Comment 69 (CERT; NCA[651]): Among the studies provided by CERT, one epidemiological study (Park et al. 2018)[652] and one meta-analysis (Han and Kim 2017)[653] were released after the IARC 2016 report. NCA also referenced these two studies.

CERT also discusses studies on thyroid cancer and smoking, noting inverse dose response relationships. This is in the section entitled "OEHHA's claim that coffee is unique", in the subsection, "Coffee and smoking are associated with reduced risk of certain cancers" (XI.A.4). CERT states, "Consumption of coffee and cigarette smoking have both been inversely associated with … thyroid cancer. Thus, the assertion by OEHHA in its Initial Statement of Reasons that '[c]offee is unique in that it shows reductions in certain human cancers' is incorrect."

One prospective cohort study (Hashibe et al. 2015[654]) and one additional meta-analysis (Franceschi et al. 1991[655]) were released earlier and were not included in the Monograph but were referenced by CERT as examples of coffee being associated with reduced risk of cancer.

[650] IARC (2018), full citation provided in footnote 3, p. 419.
[651] CERT 18, pp. 304-307; NCA, pp. 19, 52
[652] Park et al. (2018), full citation provided in footnote 504.
[653] Han MA, Kim JH (2017). Coffee consumption and the risk of thyroid cancer: A systematic review and meta-analysis. *Int. J. Environ. Res. Public Health* 27;14(2).
[654] Hashibe M, Galeone C, Buys SS, Gren L, Boffetta P, Zhang ZF, La Vecchia C (2015). Coffee, tea, caffeine intake, and the risk of cancer in the PLCO cohort. *Br. J. Cancer* 113(5):809-816.
[655] Franceschi S, Levi F, Negri E, Fassina A, La Vecchia C (1991). Diet and thyroid cancer: A pooled analysis of four European case-control studies. *Int. J. Cancer*: 48, 395-398.

Response 69: First, with regard to smoking and thyroid cancer, OEHHA notes in IARC's most recent Monograph on Tobacco Smoking[656], thyroid was one of two cancers for which IARC found lack of evidence of carcinogenicity from tobacco smoke.

Regarding the studies commented on by CERT and NCA:

- Park et al. (2018) was a prospective cohort study[657] that evaluated the association between coffee consumption with overall cancer incidence and specific cancer sites in a large prospective study of 167,720 African Americans, Native Hawaiians, Japanese Americans, Latinos and whites in the US Multiethnic Cohort (MEC) of Hawaii and Los Angeles assembled in 1993–1996. Coffee intake was associated inversely with thyroid cancer (HR = 0.44, 95% CI: 0.23–0.87, *p* trend: 0.007).

- Han and Kim (2017)[658] was a meta-analysis that included 1,039 thyroid cancer cases and 220,816 controls from two cohort studies and five case-control studies. There was no association between coffee consumption and thyroid cancer risk overall (OR = 0.88, 95% CI: 0.71–1.07). An inverse association was observed in the hospital-based case-control studies (OR = 0.59, 95% CI: 0.37–0.93). All of the studies were evaluated in IARC (2018) except two case-control studies[659,660]. Riza et al. (2015)[661] was a hospital-based case-control study in Greece that found no association of coffee consumption with benign or malignant thyroid cancer. Galanti et al. (1997)[662] was a population-based case-control study in Sweden and Norway that found no association of coffee consumption with thyroid cancer.

Regarding the older studies referenced by CERT:

- Franceschi et al. (1991)[663], submitted by CERT, was a pooled analysis of four hospital-based case-control studies in Italy and Switzerland that found that coffee

[656] IARC (2012a), full citation provided in footnote 146, pp. 108 and 167, Available at: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100E-6.pdf.
[657] Park et al. (2018), full citation provided in footnote 504.
[658] Han and Kim (2017), full citation provided in footnote 653.
[659] Riza E, Linos A, Petralias A, de Martinis L, Duntas L, Linos D (2015). The effect of Greek herbal tea consumption on thyroid cancer: a case-control study. *European Journal of Public Health* 25:1001-1005.
[660] Galanti MR, Hansson L, Bergstrom R, Wolk A, Hjartaker A, Lund E et al. (1997). Diet and the risk of papillary and follicular thyroid carcinoma: a population-based case-control study in Sweden and Norway. *Cancer Causes and Control* 8:205-214.
[661] Riza et al. (2015), full citation provided in footnote 659.
[662] Galanti et al. (1997), full citation provided in footnote 660.
[663] Franceschi et al. (1991), full citation provided in footnote 655.

consumption was associated with a decreased risk of thyroid cancer. However, no confidence intervals were reported in this study.

- Hashibe et al. (2015)[664], referenced by CERT, was a prospective cohort study in the Prostate, Lung, Colorectal, and Ovarian cancer screening trial. There was no association between consumption of ⩾2 cups of coffee/day compared to none with thyroid cancer (RR = 1.00, 95% CI: 0.65 – 1.53, *p* trend: 0.9801).

The IARC (2018) summary stated, "The sparse evidence available for [cancer of the thyroid] did not permit conclusions to be drawn,"[665] and concluded there was inadequate evidence of carcinogenicity for the thyroid. While the additional studies overall show inverse relationships, the evidence remains sparse and consistent with IARC's original conclusion.

No changes to the proposed regulation were made based on this comment.

Uterine endometrial cancer

Comment 70 (CERT; NCA[666]): Under the heading "Consistency of results" in section VI.A on "OEHHA's claim that coffee prevents cancer in women", CERT states:

> "Although epidemiologic studies regarding consumption of coffee and endometrial cancer have generally reported inverse associations, the results of the studies are not entirely consistent."

CERT then discusses several studies, all of which were discussed in IARC (2018) with the exception of two studies, Ding et al. (2015)[667] and Gunter et al. (201[7])[668].

[664] Hashibe et al. (2015), full citation provided in footnote 654.
[665] IARC (2018), full citation provided in footnote 3, p. 420.
[666] CERT 18, pp. 91-94; 292-295; NCA, pp. 48-51
[667] Ding M, Satija A, Bhupathiraju SN, Hu Y, Sun Q, Han J et al. (2015). Association of coffee consumption with total and cause-specific mortality in 3 large prospective cohorts. *Circulation* 132(24):2305-2315.
[668] OEHHA notes that the comment discusses the published study report by Gunter et al. 2017, but provides the wrong journal volume, issue, page numbers and year of publication. The correct citation is: Gunter MJ, Murphy N, Cross AJ, Dossus L, Dartois L, Fagherazzi G et al. (2017). Coffee drinking and mortality in 10 European countries: a multinational cohort study. *Ann. Intern. Med.* 167(4):236-247.

NCA provided one case-control study[669] and two meta-analyses[670,671] published after the IARC review, and stated, "Only one study reported that their conclusions remained unclear; the remainder concluded inverse relationships (higher coffee consumption was associated with lower cancer risk)."

Response 70: OEHHA reviewed the additional studies provided by the commenters, and makes these brief observations:

- Ding et al. (2015)[672], referenced by CERT, was a cohort study that investigated the consumption of coffee with risk of mortality among women in the Nurses' Health Study. Coffee consumption was not associated with an increased risk of endometrial cancer mortality, but among never smokers, there was a non-statistically significant elevated risk estimate.
- Gunter et al. (2017)[673], referenced by CERT, reported on findings from the large European Prospective Investigation into Cancer and Nutrition (the EPIC cohort), and found a reduced – but not statistically significant – risk for endometrial cancer mortality with coffee consumption, after adjusting for smoking.
- Rossi et al. (2016)[674], referenced by NCA, was a hospital-based case-control study conducted in Italy with 454 cases and 908 controls. This study investigated the association between total antioxidant capacity from the diet and endometrial cancer risk. In analyses where total antioxidant capacity from coffee alone was assessed, there were no associations with endometrial cancer. However, this study did not adjust for tobacco smoking. OEHHA notes that IARC (2018)[675] included only studies that adjusted for smoking and BMI, since they are important confounders in the association between coffee and uterine endometrial cancer.
- Lafranconi et al. (2017)[676] and Lukic et al. (2018a)[677] were meta-analyses referenced by NCA that found coffee consumption was associated with decreased risk of endometrial cancer. All of the individual studies in these meta-analyses were evaluated in IARC (2018).

[669] Rossi M, Tavani A, Ciociola V, Ferraroni M, Parpinel M, Serafini M et al. (2016). Dietary total antioxidant capacity in relation to endometrial cancer risk: a case-control study in Italy. *Cancer Causes Control* 27:425-31.
[670] Lafranconi A, Micek A, Galvano F, Rossetti S, Del Pup L, Berretta M et al. (2017). Coffee decreases the risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. *Nutrients* 9: doi:10.3390/nu9111223.
[671] Lukic M, Guha N, Licaj I, van den Brandt P, Stayner LT, Tavani A et al. (2018a). Coffee drinking and the risk of endometrial cancer; an updated meta-analysis of observational studies. *Nutrition and Cancer* 70:513-28.
[672] Ding et al. (2015), full citation provided in footnote 667.
[673] Gunter et al. (2017), full citation provided in footnote 345.
[674] Rossi et al. (2016), full citation provided in footnote 669.
[675] IARC (2018), full citation provided in footnote 3, p. 241.
[676] Lafranconi et al. (2017), full citation provided in footnote 670.
[677] Lukic et al. (2018a), full citation provided in footnote 671.

As explained in the IARC summary, the evidence for endometrial cancer consistently suggests an inverse or a null association.

Comprehensive reviews by other authoritative expert panels that have also assessed the evidence have made findings consistent with IARC's finding of an inverse association of risk for endometrial cancer with drinking coffee. As noted in the Response to Comment 18, the Continuous Update Project expert panel found that

> "There is strong evidence that … consumption of coffee DECREASES the risk of endometrial cancer."

The Continuous Update Project explains:

> "The mechanisms linking coffee consumption to a decrease in endometrial cancer risk remain unclear but may involve lower circulating levels of bioavailable sex steroids or insulin and higher insulin sensitivity in people who drink coffee. Coffee drinking is correlated with higher levels of sex hormone-binding globulin (SHBG), which may decrease exposure to bioavailable oestradiol levels. A large cross-sectional study of more than 1,200 women in the Nurses' Health Study reported that in premenopausal women, coffee intake was associated with lower luteal phase total and free ostradiol levels, while in postmenopausal women caffeine and coffee intake were positively associated with SHBG levels. Coffee drinking is also associated with reduced insulin levels, particularly among overweight women, and it has been hypothesised that coffee may reduce the risk of endometrial cancer through an insulin-mediated mechanism. Coffee has also been shown to alter adipokines and inflammatory pathways and lead to an increase in adiponectin levels – an adipokine that is down-regulated in obesity and has been linked to endometrial cancer development."[678]

OEHHA finds that these additional studies all show null or inverse associations and align with the overall conclusions of the IARC (2018) review, as well as the Continuous Update Project.

No changes to the proposed regulation were made based on this comment.

[678] WCRF-AICR (2018), full citation provide in footnote 69, relevant pages available at: https://www.wcrf.org/dietandcancer/exposures/non-alcoholic-drinks

Comment 71 (CERT[679]): "The Wang 2016 meta-analysis reported a reduced risk for endometrial cancer (as well as many other cancer sites) in relation to coffee consumption. The study, however, does not provide the basis for selection of studies to be included, nor indicate the studies that were rejected and the basis for the rejection. The study results are difficult to interpret as the methodology is not clearly presented. Also, Figure 1 which indicates the potential number of articles identified for inclusion in the study along with the number of excluded studies do not add up and it is difficult to know from which group the '1,997' excluded studies were excluded. Further, 'S' Table 3b titled 'female genital organs' presents results for breast cancer only, which is not a cancer of female genital organs." [680]

Response 71: The meta-analysis by Wang et al. (2016) did, in fact, describe their study inclusion and exclusion criteria in the methods section on page 2 of the report. The methodology of their statistical analyses is thoroughly explained on page 3 of the paper, including the methods used to calculate overall relative risks, dose-response analyses, and evaluation of study heterogeneity and publication bias. "Stable" (or Supplemental table) 3b presents results for endometrial cancer after the results for breast cancer and ovarian cancer. It is true that the female breast is not a genital organ; however, it appears that the authors are grouping by female-specific cancers. Regarding Figure 1, of the 1,503 articles identified for further review plus the 600 references identified from searching the references of identified articles (1,503 + 600), 1,997 articles were excluded, leaving 106 (1,503 + 600 – 1,997 = 106). The figure shows "2 cohorts was (sic) overlapping" with an arrow indicating they were removed. However, the final number is 105 articles, and it can be assumed that one of those overlapping articles was removed, bringing the total from 106 to 105.

No changes to the proposed regulation were made based on this comment.

Comment 72 (CERT[681]): CERT made several statements regarding confounding of endometrial cancer and coffee associations by cigarette smoking:

> "All of the epidemiologic studies regarding coffee consumption and endometrial cancer are negatively confounded by cigarette smoking to some degree, most being substantially confounded."

[679] CERT 18, p. 295
[680] Wang et al. (2016), full citation provided in footnote 206.
[681] CERT 18, pp. 95-96, 292-296; CERT H1, transcript pp. 29-30, 40

"[S]everal prospective investigations have reported inverse associations between cigarette smoking and endometrial cancer, a finding that has been attributed to possible anti-estrogenic effects of tobacco smoke." (Gunter 2010)[682]

"Even though some studies that have adjusted for smoking have found significantly decreased risks of endometrial cancer related to coffee consumption, a residual effect from cigarette smoking is still a likely confounder, just as increased risks of lung cancer in coffee drinkers are likely confounded by cigarette smoking, even though some studies that adjusted for cigarette smoking demonstrate elevated risks of lung cancer in relation to coffee consumption."

"So the positive association between coffee consumption and lung cancer is generally thought to be due to residual confounding by smoking, which is highly correlated with coffee consumption. But likewise, the negative association between coffee consumption and endometrial cancer is probably due to confounding by smoking, because cigarette smoking reduces the risk of endometrial cancer by more than 50 percent, just like coffee. And they're highly correlated. Nobody seems to consider that.

"Oh, coffee prevents endometrial cancer. Reduces the risk 50 percent. OEHHA totally failed to consider negative confounding by cigarette smoke as a biologically plausible explanation for the inverse association between coffee consumption and endometrial cancer. OEHHA simply assumed that coffee consumption prevents endometrial cancer."

Response 72: IARC's evaluation of cancer of the endometrium states, "As BMI and smoking are important confounders, studies not adjusting for these factors (Jacobsen et al. 1986; Levi et al. 1993b; Stensvold & Jacobsen 1994; Goodman et al. 1997; Bravi et al. 2009b[683]) were considered uninformative and were excluded from further review."[684]

[682] Gunter MJ (2010) Re: coffee drinking and risk of endometrial cancer--a population-based cohort study. *Int J Cancer.* 126(7):1770.
[683] Jacobsen BK, Bjelke E, Kvåle G, Heuch I (1986). Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. *J. Natl. Cancer Inst*, 76(5):823–31; Levi F, Franceschi S, Negri E, La Vecchia C (1993). Dietary factors and the risk of endometrial cancer. *Cancer* 71(11):3575–81; Stensvold I, Jacobsen BK (1994). Coffee and cancer: a prospective study of 43,000 Norwegian men and women. *Cancer Causes Control* 5(5):401–8; Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ et al. (1997). Diet, body size, physical activity, and the risk of endometrial cancer. *Cancer Res.* 57(22):5077–85; Bravi F, Scotti L, Bosetti C, Zucchetto A, Talamini R, Montella M et al. (2009). Food groups and endometrial cancer risk: a case-control study from Italy. *Am. J. Obstet. Gynecol*. 200(3):293.e1–7.
[684] IARC (2018), full citation provided in footnote 3.

Additionally, two large meta-analyses published after IARC's review conducted subgroup analyses by smoking status.

Lafranconi et al. (2017) found similar risk estimates comparing never smokers and ever smokers. Both of these were similar to the risk estimate found in the analysis that included studies that adjusted for smoking:

Never smokers: RR = 0.78 (95% CI: 0.68–0.88, 8 datasets)
Ever smokers (former/current): RR = 0.74 (95% CI: 0.57–0.98, 8 datasets)
Studies that adjusted for smoking: RR = 0.79 (95% CI: 0.73–0.87, 10 datasets)[685]

Lukic et al. (2018a) found similar negative associations for cancer of the endometrium with coffee consumption for never smokers, former smokers, current smokers, and ever smokers:

Never smokers: RR = 0.78 (95% CI: 0.67–0.92, 6 datasets)
Former smokers: RR = 0.80 (95% CI: 0.66–0.97, 2 datasets)
Current smokers: RR = 0.71 (95% CI: 0.22–2.25, 2 datasets)
Ever-smokers: RR = 0.67 (95% CI: 0.49–0.92, 5 datasets)[686]

These results are overall consistent with several cohort studies that also did not find differences in strata of smoking (see IARC's discussion of Friberg et al. 2009; Weiderpass et al. 2014; Gunter et al. 2012; Uccella et al. 2013; Yang et al. 2015[687]). These studies that stratified analyses by smoking status provide further evidence that the findings of reductions in endometrial cancer risk associated with coffee drinking cannot be explained by residual confounding by smoking.

No changes to the proposed regulation were made based on this comment.

[685] Lafranconi et al. (2017), full citation provided in footnote 670.
[686] Lukic et al. (2018a), full citation provided in footnote 671.
[687] Friberg E, Orsini N, Mantzoros CS, Wolk A (2009). Coffee drinking and risk of endometrial cancer–a population-based cohort study. *Int. J. Cancer* 125(10):2413–7; Weiderpass E, Sandin S, Lof M, Oh JK, Inoue M, Shimazu T et al. (2014). Endometrial cancer in relation to coffee, tea, and caffeine consumption: a prospective cohort study among middle-aged women in Sweden. *Nutr. Cancer* 66(7):1132–43; Gunter MJ, Schaub JA, Xue X, Freedman ND, Gaudet MM, Rohan TE et al. (2012). A prospective investigation of coffee drinking and endometrial cancer incidence. *Int. J. Cancer* 131(4):E530–6; Uccella S, Mariani A, Wang AH, Vierkant RA, Cliby WA, Robien K et al. (2013). Intake of coffee, caffeine and other methylxanthines and risk of Type I vs Type II endometrial cancer. *Br. J. Cancer* 109(7):1908–13; Yang TO, Crowe F, Cairns BJ, Reeves GK, Beral V (2015). Tea and coffee and risk of endometrial cancer: cohort study and meta-analysis. *Am. J. Clin. Nutr.* 101(3):570–8.

Overall cancer

Comment 73 (CERT; NCA[688]): CERT's introduction of studies was made in the section "Coffee consumption increases the risk of several cancers," subsection "Meta-analyses" (V.B.11). CERT stated, "The epidemiological studies regarding coffee consumption and total cancer mortality do not indicate an inverse association between coffee consumption and mortality from cancer."

Studies briefly described by both CERT and NCA that were released after the IARC meeting include one epidemiological study[689] on all-sites cancer, four studies[690,691,692,693] on cancer mortality, and one review[694]. In addition, NCA also referenced three studies[695,696,697] on cancer mortality that were released after the IARC meeting.

Response 73:

- Sado et al. (2017)[698], submitted by CERT and referenced by NCA, was a prospective cohort study that followed 39,685 men and 43,124 women for 15 years. This study found an inverse association between coffee consumption and all-sites cancer incidence for participants who consumed ≥5 cups/day (HR = 0.74, 95% CI: 0.62–0.88, *p* trend < 0.001 for men; HR = 0.76, 95% CI: 0.58–1.02, *p* trend: 0.020 for women). Coffee consumption frequency was also inversely associated with mortality from all-sites cancer.
- Gapstur et al. (2017)[699], submitted by CERT, was a large prospective cohort study that followed 922,896 Cancer Prevention Study-II participants from 1982 through 2012. In analyses that adjusted for multiple variables and stratified on

[688] CERT 18, pp. 77-81, 286; NCA, pp. 19-22
[689] Sado J, Kitamura T, Kitamura Y, Sobue T, Nishino Y, Tanaka H et al. (2017). Association between coffee consumption and all-sites cancer incidence and mortality. *Cancer Sci.* 108:2079-2087.
[690] Gapstur et al. (2017), full citation provided in footnote 148.
[691] Gunter et al. (2017), full citation provided in footnote 345. OEHHA notes that the comment (CERT 18, pp. 80-81) discusses the published study by Gunter et al. (2017), but provides the wrong journal volume, issue, page numbers and year of publication.
[692] van den Brandt P (2018). Coffee or tea? A prospective cohort study on the associations of coffee and tea intake with overall and cause-specific mortality in men versus women. *Eur. J. of Epidemiol.* 33:183-200.
[693] Grosso G, Micek A, Godos J, Sciacca S, Pajak A, Martínez-González MA et al. (2016a). Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis. *Eur. J. Epidemiol.* 31:1191-1205.
[694] Pourshahidi LK, Navarini L, Petracco M, Strain JJ. (2016) A Comprehensive Overview of the Risks and Benefits of Coffee Consumption. *Compr. Rev. Food Sci. F.* 15:671-684.
[695] Grosso G, Stepaniak U, Micek A, Stefler D, Bobak M, Pajak A (2016b). Coffee consumption and mortality in three Eastern European countries: results from the HAPIEE (Health, Alcohol and Psychosocial factors In Eastern Europe) study. *Public Health Nutrition* 20(1):82-91.
[696] Carrieri MP, Protopopescu C, Marcellin F, Rosellini S, Wittkop L, Esterle L (2017). Protective effect of coffee consumption on all-cause mortality of French HIV-HCV co-infected patients. *J. Hepatol.* 67:1157-67.
[697] Nordestgaard AT and Nordestgaard BG (2016). Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analyses in 95,000-223,000 individuals. *Int. J. Epidemiol.* 45:1938-1952.
[698] Sado et al. (2017), full citation provided in footnote 689.
[699] Gapstur et al. (2017), full citation provided in footnote 148.

smoking status, there was no association between coffee consumption and risk of death from all cancers among never smokers. Among former smokers, the association between coffee consumption and risk was nonlinear, with no clear pattern of association in the categorical multivariable-adjusted analysis.

- Gunter et al. (2017)[700], submitted by CERT, was a prospective cohort study with a 16.4-year mean follow-up within the EPIC cohort, which investigated the association between coffee drinking and mortality, including overall cancer mortality. The study found no association between coffee drinking and all-cancer mortality in both sexes combined or in men. In women, the risk of death from all cancers in the highest quartile of coffee consumption compared to nondrinkers was increased (HR = 1.03, 95% CI: 1.01–1.04), but was not significant in never smokers (HR = 1.01, 95% CI: 0.99–1.04).
- van den Brandt (2018)[701], referenced by CERT and NCA, was a case-cohort study that analyzed data from the Netherlands Cohort Study. Coffee intake was positively associated with death due to cancer in men (HR = 1.49, 95% CI: 1.04–2.13) when comparing six or more to 0-1 cups/day with a trend of borderline statistical significance (*p* trend = 0.06). An inverse association was observed in women with statistically significantly decreased HRs in several intake categories (HR = 0.65, 95% CI: 0.44–0.95) when comparing 5–<6 versus 0–1 cups/day.
- Grosso et al. (2016a)[702], submitted by CERT and referenced by NCA, was a meta-analysis that included 15 studies on cancer mortality. No associations were observed between coffee consumption and risk of death from cancer. In non-smokers, a statistically significantly decreased risk of death from cancer was observed (RR = 0.98, 95% CI: 0.96–1.00).
- Pourshahidi et al. (2016)[703], the review submitted by CERT and referenced by NCA, did not include any epidemiological studies on coffee and cancer risk that were not reviewed by IARC (2018).
- Grosso et al. (2016b)[704], referenced by NCA, was a prospective cohort study on mortality in the Health, Alcohol and Psychosocial factors In Eastern Europe study. Coffee consumption was not associated with risk of death from cancer in men or women in multivariable adjusted models.
- Carrieri et al. (2017)[705], referenced by NCA, was a prospective cohort study that investigated the relationship between coffee consumption and the risk of all-cause mortality in patients co-infected with HIV and HCV. The study did not separately assess cancer mortality.

[700] Gunter et al. (2017), full citation provided in footnote 345.
[701] van den Brandt (2018), full citation provided in footnote 692.
[702] Grosso et al. (2016a), full citation provided in footnote 693.
[703] Pourshahidi et al. (2016), full citation provided in footnote 694.
[704] Grosso et al. (2016b), full citation provided in footnote 695.
[705] Carrieri et al. (2017), full citation provided in footnote 696.

- Nordestgaard and Nordestgaard (2016)[706], referenced by NCA, was a Mendelian randomization study that assessed coffee intake, cardiovascular disease and all-cause mortality. It did not analyze cancer-specific mortality.

With the exception of van den Brandt (2018) and Gunter et al. (2017), which found positive associations in subgroup analyses, these studies report null or inverse associations between coffee consumption and overall cancer risk.

IARC noted in its review that:

> "The association between coffee consumption and the occurrence of all cancers combined has been investigated in a number of prospective cohort studies from Europe, Japan, and North America. Most studies found no association between coffee consumption and incidence … or mortality … of all cancers combined, with no exposure–response trends and no statistically significant overall increase or decrease in risk among the heaviest consumers. One study reported non-significantly increased mortality from all cancers among men who drank $\geqslant$ 6 cups/day of coffee with a significant trend … but no association among women. Another study that found no association with cancer mortality in the full cohort reported increased mortality in a subgroup of women aged > 50 years consuming > 5 cups/day of coffee …. A statistically significant inverse exposure– response trend … was reported for cancer mortality among women, but not men, in a study by Tamakoshi et al. (2011). ..Two meta-analyses of prospective studies estimated null associations between coffee consumption and mortality from all cancers combined …"[707]

OEHHA finds that the results of these more recent studies are in line with the evidence that IARC considered for all cancer mortality and incidence.

No changes to the proposed regulation were made based on this comment.

[706] Nordestgaard and Nordestgaard (2016), full citation provided in footnote 697.
[707] IARC (2018), full citation provided in footnote 3, p. 310.

SUMMARY OF PUBLIC COMMENTS AND RESPONSES ON THE AMENDMENTS TO THE PROPOSED REGULATION

A summary of the relevant comment received during the second public comment period from March 15, 2019 to April 2, 2019 is provided below, along with OEHHA's response to that comment. Additionally, on April 1, 2019, OEHHA received a submission from CERT requesting that OEHHA extend the comment period an additional 15 to 30 days and provide an explanation of the reasons for proposing the textual modification. OEHHA pointed out in replying to CERT that the explanation for the proposed textual modification was included in OEHHA's March 15, 2019, Notice of Modification. OEHHA denied the request to extend the comment period but notified CERT that OEHHA would consider any relevant comments submitted by CERT before April 8, 2019 at 5:00 pm. CERT did not submit any comments relevant to the proposed textual modification.

Comment 74 (NCA): The modified regulatory text, like the original proposed text, is within OEHHA's statutory authority but limiting the regulation to those chemicals listed as of March 15, 2019, is unnecessary. Nevertheless, the NCA supports the modified proposal.

Response 74: OEHHA acknowledges commenter's continued support for the proposed regulation. As stated in our March 15, 2019, Notice of Modification, OEHHA modified the language of the proposed regulatory text to clarify the scope of listed chemicals covered by the proposed regulation. The date chosen is the date the public comment period for the proposed modification began. This avoids any confusion that could occur if OEHHA were to list a chemical that occurs in coffee between the date of the Notice and the effective date of the regulation.

No changes to the proposed regulation were made based on this comment.

EXTERNAL SCIENTIFIC PEER REVIEW COMMENTS AND RESPONSES

Comment 75 (Drs. Bush, Dairkee, Landolph, and McDonald): Peer reviewers state support for the proposed regulation.

Dr. Bush stated that the rationale for the proposed regulation "seems logical and consistent with the considerable scientific evidence and the comprehensive review by IARC," and that he agrees with OEHHA's conclusion that exposures to listed chemicals in coffee pose no significant risk.

Dr. Dairkee stated, "Upon reviewing the available scientific literature on the association between coffee consumption and cancer risk, I concur with the assessment of OEHHA scientists that an adverse role for coffee intake in cancer development and progression has not been established to date."

Dr. Landolph stated he carefully reviewed the ISOR, the IARC 2018 Monograph, and available scientific literature. He stated that the ISOR is "well-researched, well-written, very interesting, and makes the salient points that coffee contains many carcinogens, but also contains many anti-oxidants and anti-carcinogens", that OEHHA "came to the correct opinions and conclusions", and that "the ISOR is acceptable for indicating coffee drinking poses no significant risk of cancer."

Dr. McDonald wrote that he reviewed both the ISOR and the IARC 2018 Monograph, and then stated, "I agree with the conclusion that drinking coffee does not result in an overall increased risk of cancer in the California population. I further agree with OEHHA's proposed regulation that exposures to coffee constituents that are listed on Proposition 65 do not pose a significant cancer risk when consumed as coffee."

Response 75: OEHHA acknowledges the comments.

Comment 76 (Dr. Landolph and Dr. Mack): Peer reviewers suggested clarification of the proposed regulatory language to reflect that the proposed regulation only covers exposure to carcinogens in coffee through consuming coffee, but not exposures to any of the carcinogens from other sources.

On page 2 of his comment, Dr. Landolph asked OEHHA to add clarifying phrases "and drinking coffee" to page 3, paragraph 1, line 7 of the ISOR, so that this line reads "…brewing coffee and drinking coffee pose no significant risk of cancer". He also suggested modifying lines 11 and 12 of the last sentence of this paragraph to "…other

than the inherent process of roasting coffee beans, brewing coffee, and drinking this coffee."

Dr. Mack emphasized that the carcinogens in coffee "ARE still carcinogens", and "the phraseology should always be that coffee is safe, and NOT that the chemicals in coffee are safe".

Response 76: OEHHA agrees with the peer reviewers that the proposed regulatory text refers to exposures to Proposition 65 carcinogens in coffee that are created by and inherent in the processes of roasting or brewing coffee *that occur as a result of consuming coffee*. This regulation does not apply to exposures to these carcinogens from other sources (e.g., it does not apply to exposure to benzo(a)pyrene present in tobacco smoke, or to exposure to acrylamide in French fries).

Dr. Mack's comment also suggests use of the term "safe" (i.e., "coffee is safe"). Through this rulemaking, however, OEHHA has considered only the risk of cancer and not other health endpoints that may be related to coffee consumption. Accordingly, OEHHA has not considered, or determined, whether coffee is safe. Nor has OEHHA concluded that the carcinogens in coffee are safe, as the commenter suggests. Rather, the proposed regulation is based on OEHHA's determination that exposures to carcinogens in coffee (that are created by and inherent in the processes of roasting or brewing coffee and that occur through the consumption of coffee) *pose no significant risk of cancer*.

No changes to the proposed regulation were made based on this comment.

Comment 77 (Dr. Landolph): Additional studies

Dr. Landolph suggested that the following studies be included as references:

- Berretta et al. (2018)[708]
- Torres-Collado et al. (2018)[709]
- Arthur et al. (2018)[710]
- Islam et al. (2018)[711]

[708] Berretta et al. (2018), full citation provided in footnote 544.
[709] Torres-Collado L, Garcia-d-la-Hera M, Navarette-Munoz EM, Notario-Barandiaran L, Gonzalez-Palacios S, Zurriaga O et al. (2018). Coffee consumption and mortality from all causes of death, cardiovascular disease, and cancer in an elderly Spanish population. *Eur. J. Nutr.* doi: 10.1007/s00394-018-1796-9. [Epub ahead of print]
[710] Arthur et al. (2018), full citation provided in footnote 245.
[711] Islam MT, Tabrez S, Jabir NR, Ali M, Kamal MA, Da Silva Araujo L et al. (2018). An insight into the therapeutic potential of major coffee components. *Current Drug Metabolism* 19:544-556.

Response 77: OEHHA appreciates the information on these studies, and has reviewed and summarized them as follows:

Berretta et al. (2018) is a meta-analysis of prospective cohort studies on coffee and the risk of ovarian cancer identified in the published literature as of March 2017. This meta-analysis included nine epidemiological studies, and all of them were reviewed by IARC (2018). Berretta et al. (2018) concludes that "coffee intake was not associated with ovarian cancer risk", which is consistent with IARC's evaluation that the majority of the cohort and case-control studies on ovarian cancer suggest no association (p. 419, IARC 2018).

Torres-Collado et al. (2018) is a population-based prospective cohort study on the association between coffee consumption and cancer mortality among 905 elderly participants of the EUREYE-Spain study and Valencia Nutrition survey in Spain with a 12-year follow-up. The study found no association between coffee consumption (both caffeinated and decaffeinated) and cancer mortality in a multivariable model that adjusted for age and sex and in a multivariable model that adjusted for smoking and a number of other factors.

Arthur et al. (2018) is a prospective cohort study of 3,185 Canadian women that investigated the association between coffee intake and risks of breast, endometrial, and ovarian cancers, with a median 12.2-year follow-up. The study found:

- No association between coffee (total coffee, caffeinated coffee, and caffeine) and risk of ovarian cancer
- Inverse association between coffee intake (total coffee, caffeinated coffee, and caffeine) and endometrial cancer
- No associations between coffee, tea, and caffeine intake and risk of breast cancer overall, but an increased hazard ratio (HR) in women drinking 3-4 cups of caffeinated coffee that were premenopausal or had a BMI>25. However, risk was not increased in women drinking more than four cups that were premenopausal or had a BMI>25. Thus the results were inconsistent.

Islam et al. (2018) is a review of the pharmacological activities of coffee components, including antioxidant, anti-inflammatory, anti-microbial, and many other activities.

Torres-Collado et al. (2018) and Arthur et al. (2018) were published after the ISOR was published. Berretta et al. (2018) is a meta-analysis of studies that were all included in the IARC review. Islam et al. (2018) is one of many reviews of the pharmacological activities of coffee components. These publications are all compatible with the proposed regulation.

No changes to the proposed regulation were made based on OEHHA's review of these studies.

Comment 78 (Dr. Landolph, p. 2-3 and Dr. Mack): Reviewers asked OEHHA to discuss why drinking coffee is not associated with increased cancer risk, despite the presence of multiple carcinogens in coffee.

Dr. Landolph asked OEHHA to discuss why "since coffee contains many carcinogens, it is not carcinogenic when administered to humans by the drinking water route", and to discuss the mechanisms of the carcinogenicity of this mixture of different classes of carcinogens. Dr. Landolph also states that it is important to set forth some hypotheses to explain why drinking coffee is not associated with increased cancer risk, and he suggests several possible hypotheses.

Dr. Mack asked OEHHA to explain "why one wouldn't expect the carcinogens in coffee to result in identifiable cancers". Dr. Mack goes on to say, "They [carcinogens in coffee] ARE still carcinogens, and while there may be interaction, that is sheer speculation." "The safety of coffee is presumably a matter of dose…". Dr. Mack suggested that OEHHA add a statement like "at the doses in coffee, the chemicals are safe".

Response 78: OEHHA appreciates the suggestions and hypotheses Dr. Landolph and Dr. Mack provided to explain why drinking coffee is not associated with a significant increase in cancer risk, despite the presence of multiple carcinogens in coffee. Coffee is a complex mixture that contains many constituents with a variety of biological activities. The ways in which these chemicals interact in individuals that drink coffee (e.g., antagonistic, synergistic) is not fully understood. OEHHA chose to rely on empirical data from studies in humans and experimental animals that have investigated the relationship between drinking coffee and risk. See Responses to Comments 15, 25, 26, 27.

No changes to the proposed regulation were made based on this comment.

Comment 79 (Dr. Mack): Dr. Mack states that OEHHA's emphasis on coffee's protective qualities is irrelevant to OEHHA's mandate and is a completely separate process from determining carcinogenicity. He also stated, "If it actually prevents, it does not do it by turning off a carcinogenic event, but by modifying the level of susceptibility to such an event." He then gave the example of the recognized human carcinogen tamoxifen, which despite its action to reduce the risk of breast cancer, still causes uterine endometrial cancer in women.

Response 79: OEHHA's mandate is to implement Proposition 65, including through the adoption of regulations to further its purpose. (Health and Safety Code, 25249.12(a).) The proposed regulation identifies particular exposures to listed chemicals that do not pose a significant risk of cancer, which furthers the purpose of Proposition 65 because the statute's warning requirement does not apply to the extent it can be shown that an exposure to a listed carcinogen poses no significant risk of cancer to the average consumer. (*Id.,* 25249.10(c); Cal. Code Regs., tit. 27, 25721(d)(4).) Accordingly, adopting the proposed regulation falls within OEHHA's mandate.

With respect to the question of how, or why, coffee does not pose a significant risk of cancer, as noted above, coffee is a complex mixture that contains many constituents with a variety of biological activities, including carcinogens and chemicals that have properties associated with reduced cancer risk. The ways in which these chemicals interact in individuals that drink coffee (e.g., antagonistic, synergistic) is not fully understood.

The level of evidence of carcinogenicity for coffee, however, differs considerably from tamoxifen. For tamoxifen IARC found:

- "There is sufficient evidence in humans for the carcinogenicity of tamoxifen. Tamoxifen causes cancer of the endometrium. For cancer of the female breast, there is evidence suggesting lack of carcinogenicity. An inverse relationship has been established between exposure to tamoxifen and cancer of the female breast."
- "There is sufficient evidence in experimental animals for the carcinogenicity of tamoxifen."
- "Tamoxifen is carcinogenic to humans."[712]

In contrast, after reviewing more than 1,000 studies of coffee and cancer, IARC concluded that there is "inadequate evidence in humans for the carcinogenicity of drinking coffee", there is "inadequate evidence in experimental animals for the carcinogenicity of drinking coffee", and placed coffee in Group 3: "Not classifiable as to its carcinogenicity to humans".

IARC made additional conclusions with regard to the lack of evidence of carcinogenicity in humans for drinking coffee. Specifically, it found that "there is evidence suggesting lack of carcinogenicity of drinking coffee in humans for cancers of the pancreas, liver,

[712] International Agency for Research on Cancer (IARC 2012b). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. A Review of Human Carcinogens. Pharmaceuticals. Tamoxifen. Volume 100A, World Health Organization, Lyon, France. Available at https://monographs.iarc.fr/wp-content/uploads/2019/04/mono100A-13_new.pdf

female breast, uterine endometrium, and prostate", and "inverse associations with drinking coffee have been observed with cancers of the liver and uterine endometrium".

No changes to the proposed regulation were made based on this comment.

ALTERNATIVES DETERMINATION

In accordance with Government Code, section 11346.9(a)(4), OEHHA has considered available alternatives and determined that no reasonable alternative would be more effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action, or would be more cost effective to affected private persons and equally effective in implementing the statutory policy or other provision of law.

The only alternative to this regulatory action is to take no action. Proposition 65 states, "No person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual, except as provided in Section 25249.10."[713] The last clause provides a critical qualifier to the warning requirement, as Health and Safety Code, section 25249.10(c) exempts from the warning requirement "exposure[s] for which the person responsible can show that the exposure poses *no significant risk* assuming lifetime exposure at the level in question for substances known to the state to cause cancer…." (Emphasis added) Thus, warnings are *not* required to be given for exposures to carcinogens if the exposure poses no significant risk of cancer.

As explained in the Initial Statement of Reasons, the overwhelming scientific evidence shows that exposures to listed chemicals created by and inherent in the processes of roasting coffee beans or brewing coffee does not pose a significant cancer risk. However, the presence of Proposition 65 listed carcinogens in coffee has led to many businesses providing cancer warnings for coffee despite the evidence that coffee consumption does not pose a significant risk of cancer. As the lead agency for implementation of Proposition 65, OEHHA has the authority to "adopt and modify regulations, standards, and permits, as necessary to conform with and implement" the statute.[714] This includes promulgating regulations necessary "to implement the warning

[713] Health and Safety Code Section 25249.6
[714] Health and Safety Code Section 25249.12(a).

requirement of the Act in a reasonable manner and to facilitate compliance with the Act by defining key terms and making them more specific and relevant to the regulated business activities.*"*[715]

By defining "no significant risk" in terms of the exposures caused by consuming the complex mixture of chemicals in coffee, this proposed regulation furthers the statutory purpose of safeguarding the effectiveness of warnings by identifying an exposure that does not require a warning based on overwhelming scientific evidence. The proposed regulation therefore clarifies to businesses that cancer warnings are not required for coffee. The alternative of taking no action would leave businesses without guidance as to whether cancer warnings are required for coffee and continue the proliferation of unnecessary warnings.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. Local agencies and school districts are exempt from Proposition 65. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. The regulation clarifies that certain Proposition 65 chemicals in coffee pose no significant cancer risk, providing guidance to businesses concerning whether Proposition 65 warnings are required for coffee. This regulation does not impose a mandate.

[715] Nicolle-Wagner v. Deukmejian (1991) 230 Cal.App.3d 652, 658, quoting the Final Statement of Reasons of the challenged regulation (internal quotes omitted).