HARVARD SCHOOL OF PUBLIC HEALTH

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010
Sacramento, CA 95812-4010

Re: Potential Regulatory Action Exempting from the Proposition 65 Warning Requirements, Exposures from Chemicals that form from Natural Constituents in Food During Cooking or Heat Processing

June 2, 2005

Dear Ms. Oshita:

We appreciate the opportunity to comment on the proposed language for the exemption and we hope that our comments as experts in risk analysis and nutritional epidemiology will be helpful for OEHHA's deliberations.

We support the following proposed language: "For purposes of Health and Safety Code, section 25249.6, an exposure does not occur if the person otherwise responsible can show that the chemical in question formed solely from constituents naturally present in food and as a result of the food being cooked or heat processed, and that the concentration of the chemical in question has been reduced to the lowest level currently feasible using good cooking and manufacturing processes." We commend OEHHA for its consideration of a strategy that would avoid the significant consumer burden of additional warnings on foods containing acrylamide, a substance that occurs in many and diverse foods that collectively contribute to a balanced diet.

Although risk communication continues to evolve, several important documents provide critical guidance. The 1989 National Academy of Sciences National Research Council report focused on criteria for successful risk communication and identified several considerations that OEHHA should consider including: "The risk communication process… can be considered successful only to the extent that it, first, improves or increases the base of accurate information that decision makers use, … and second, satisfies those involved that they are adequately informed within the limits of available knowledge." (NAS-NRC, 1989, Improving Risk Communication, page 8, see also section starting on page 26). Most importantly, this report emphasized the interaction between risk communication and risk management, suggesting that OEHHA should appropriately consider the potential effects of requiring or not requiring warnings on foods that meet the criteria of the proposed language, like acrylamide. In a 1994 paper titled "Efficacy of Labeling of Foods and Pharmaceuticals" (Annual Review of Public Health, Vol. 15: 325-343), Professor Kip Viscusi provided some limited evidence to suggest that consumers significantly misperceive the risks associated with the Proposition 65 warnings and that "conveying warning information does not necessarily ensure accurate probability assessments." We believe that OEHHA should conduct research to evaluate the impact of Prop 65 warnings, particularly given

the apparent lack of empirical evidence we find available in the peer-reviewed literature about how the warnings impact consumers perceptions, attitudes, and behaviors. We suggest that OEHHA should at a minimum verify that any warnings added to a large portion of the food supply do not in effect lead to nutritional deficiencies. Given relatively recent fortification of the flour supply with folate to reduce neural tube defects (women need sufficient folate in weeks 4-6 of pregnancy), we believe that the state should consider the impact of putting Prop 65 warnings on fortified foods and whether such warnings could cause an increase in neural tube defects for pregnant women who heeded the warnings.

The challenges with acrylamide stem from its ubiquity in heat-processed foods, the limits of our knowledge on the health effects of acrylamide in humans, and the lack of options available to further manage the exposure.

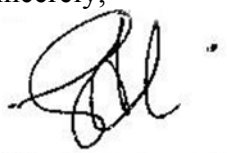
With respect to the ubiquity of acrylamide, the proposed language represents an important opportunity to avoid excessive warnings of foods. Already Californians experience myriad warnings about substances known to the state to be harmful. Adding warnings to all foods that may contain acrylamide promises to put warnings on so many foods that the net effect could be to overwhelm consumers to the point that they ignore all warnings. A recent publication notes that at least 50 different food categories have been reported to contain acrylamide and estimates that 38% of total energy in a typical US diet comes from foods containing acrylamide, with 42% of daily intake of folate comes from foods that contain acrylamide (Petersen BJ, Tran N. Exposure to acrylamide: Placing exposure in context. Adv Exp Med Biol 2005;561:63-72.) More importantly, there are likely several foods that fall within the proposed language for which there are no opportunities for either the consumer or the producer to reduce levels of acrylamide (this includes foods prepared/processed at home or by others). Thus, consumers who feel compelled to reduce their exposures may determine that their only option is to forgo a large array of foods. It is noteworthy that several of the foods that contain acrylamide also contain micronutrients and fiber that are beneficial with respect to health. From a nutritional perspective, the distortion of the diet created by extreme behavioral responses could represent a troubling possibility and we believe that OEHHA should consider the risk-risk trade-offs associated with the proposed language. In addition, if the state determines the need to put warnings on foods containing acrylamide for purposes of risk communication, then we believe it should also put warnings on foods likely to be sources of acrylamide if consumers bake or fry them at home (e.g., raw potatoes, ready-bake mixes) so as not to distort perceptions of the risks in a way that consumers only see the risks associated with foods prepared by others.

The limits of our knowledge and uncertainty about the true low dose human health effects of acrylamide also represent an important factor. Our understanding is that Californians passed Proposition 65 with the ultimate goal of improving public health. In the case of acrylamide, it may be too early to make an informed decision. Recent studies related to the human cancer risk associated with dietary exposure suggest that the risk assessments based on extrapolating high-dose animal test results to low-dose human exposures may produce misleading results. In particular, one of us (Dr. Mucci) is actively involved in research on the human epidemiological outcomes of acrylamide in the diet, most recently finding that intake of foods with elevated acrylamide was not associated with either breast or colorectal cancer risk in large, prospective studies (see attached). As noted in the attached papers, previously published case-control studies

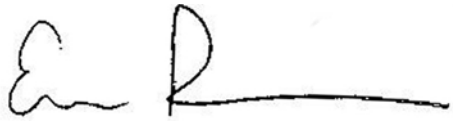
similarly found no evidence of increased risk of several cancers associated with acrylamide exposures consumed in a typical diet. Although epidemiological studies cannot exclude a small increase in cancer risk, the study results exclude a meaningful excess risk of cancer associated with dietary intake of acrylamide that could impact the public's health. The hypothesized, extrapolated effects from high dose animal tests may not provide a good indication of human risk. Not all substances that cause tumors in rats can cause tumors in humans or even mice, because the species-specific mechanisms by which cancer occurs in rodents is not relevant to humans. Significant uncertainty also exists within the risk assessment models.

Finally, we believe that failing to pass the proposed language would lead to Prop 65 warning labels on foods that would primarily serve to scare consumers and would not be a tool for risk management for those foods that would otherwise fall under the proposed language. We believe that the state should analyze the potential use of the warnings by consumers prior to requiring adding a warning to such a large number of foods for which exposure cannot be reduced, and we suspect that such an analysis would tip in favor of adding the proposed language in order to avoid information overload. We believe that the state should be very concerned that putting warnings on a large number of foods that contain acrylamide will essentially dilute the effect of warnings on other more hazardous products for which the consumers could take an action to reduce the risk, and in doing so these warnings may undermine Prop 65 overall. For all of these reasons, we believe that OEHHA should adopt the proposed language to provide the narrow exception for natural constituents in foods formed during cooking. Thank you very much for your consideration.

Sincerely,



Dr. Lorelei Mucci
Instructor in Medicine



Dr. Eric Rimm
Associate Professor of Epidemiology and Nutrition

Dr. Kimberly M. Thompson
Associate Professor of Risk Analysis and Decision Science

/attachments
Mucci et al, Int J Cancer 2005; In Press
Mucci et al, JAMA 2005 293: 1326-7

677 Huntington Avenue, 3rd Floor, Boston, MA 02115, Phone: (617) 432-4285, Fax: (617) 432-3699

A prospective study of dietary acrylamide and risk of colorectal cancer among women

Lorelei A. Mucci[1,2], Hans-Olov Adami[2,3], Alicja Wolk[4]

[1] Channing Laboratory, Brigham and Women's Hospital/Harvard Medical School, Boston, MA

[2] Department of Epidemiology, Harvard School of Public Health, Boston, MA

[3] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[4] National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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Contact Information for Corresponding Author:
Lorelei Mucci, ScD, MPH
Channing Laboratory
Brigham and Women's Hospital/Harvard Medical School
181 Longwood Avenue
Boston, MA 02115
Fax: 1 617 525 2008
Email: lmucci@hsph.harvard.edu

ABSTRACT

There has been considerable discourse about whether exposure to acrylamide in foods could increase the risk of human cancer. Acrylamide is classified as a probable human carcinogen, and animal studies have demonstrated an increased incidence of tumors in rats exposed to very high levels. Still, epidemiological data of the effect of dietary acrylamide remain scant. We have undertaken the first prospective study of acrylamide in food and risk of colon and rectal cancers using prospective data from the Swedish Mammography Cohort. The cohort comprised 61,467 women at baseline between 1987-1990. Through 2003, the cohort contributed 823,072 person-years, and 504 cases of colon and 237 of rectal cancer occurred. Mean intake of acrylamide through diet was 24.6 micrograms/day (Q25-70 = 18.7-29.9). Coffee (44%), fried potato products (16%), crisp bread (15%), and other breads (12%) were the greatest contributors. After adjusting for potential confounders, there was no association between estimated acrylamide intake and colorectal cancer. Comparing extreme quintiles, the adjusted relative risks (95% CI, p for trend) were for colorectal cancer 0.9 (0.7-1.3, p=0.80), colon cancer 0.9 (0.6-1.4, p=0.83) and rectal cancer 1.0 (0.6-1.8, p=0.77). Furthermore, intake of specific food items with elevated acrylamide (e.g. coffee, crisp bread, or fried potato products) was not associated with cancer risk. In this large, prospective study, we found no evidence that dietary intake of acrylamide is associated with cancers of the colon or rectum. Epidemiological studies play an important role in assessing the possible health effects of acrylamide intake through food.

INTRODUCTION:

There has been considerable scientific discourse over the past three years about whether exposure to acrylamide in foods could increase the risk of human cancer.[1-4] This debate first stirred in 2002 when the Swedish National Food Administration announced its initial findings of acrylamide in commonly consumed baked and fried foods. Since that time, elevated levels of acrylamide have been confirmed in several foods including cereals, crisp and soft breads, fried and baked potato products, chocolate and coffee.[5-7] Acrylamide formation occurs as a result of a chemical reaction, a Maillard process, between sugars and specific amino acids (e.g. asparagine) within foods upon exposure to high heat.[8, 9] In this way, acrylamide occurs as a natural product of cooking, rather than as a food contaminant.

The controversy about the health effects of acrylamide in humans stems from a preponderance of experimental evidence on the carcinogenicity of acrylamide, and a concomitant paucity of epidemiological data. The International Agency for Research on Cancer has classified acrylamide as a "probable human carcinogen"[10], in large part based on animal and experimental models. Animals exposed to very high levels of acrylamide have shown an increased incidence of cancer in the lung, mammary gland, oral cavity and intestinal and reproductive tract.[11] Only four epidemiological studies to date have explored whether exposure to acrylamide through diet could increase the risk of human cancer.[12-16] The evidence from these studies was converging, that intake of dietary acrylamide was not associated with an increased risk of several cancers.

Feeding studies in animals have demonstrated that high levels of acrylamide and its active metabolite, glycidamide, can be detected in the gastro-intestinal tract.[17, 18] Lifetime oncogenicity studies have demonstrated an increased incidence of intestinal tumors among rats exposed to 2-3 milligrams acrylamide per day.[19] Understanding whether dietary acrylamide

intake increases colorectal cancer risk among humans is warranted, particularly in light of the burden of this disease. Worldwide, an estimated 940,000 cases of colorectal cancer occurred in 2000, accounting for more than 9 percent of all new cases of cancer.[20] In addition, more than 481,000 deaths could be attributed to colorectal cancer during this same time period.[20] To this end, we explore in the current investigation whether dietary sources of acrylamide could increase colon and rectal cancer risk using prospective data from the Swedish Mammography Cohort.

SUBJECTS AND METHODS:

The Cohort

The source population for the present study was women eligible to participate in a population-based mammography screening program between 1987 to 1990 in two counties in central Sweden, previously described in detail[21]. Briefly, all women born between 1917 and 1948 in Västmanland County, and all women born between 1914 and 1948 in Uppsala County were invited to participate and mailed a six-page questionnaire on lifestyle and dietary factors. Of the eligible women, 66,651 (74%) returned completed questionnaires.

Excluded from the analysis were women with questionnaires containing missing or incorrect identification numbers (N=1,120), missing information about dates (N=687), with ages younger than 40 or older than 74 (N=165) or women whose dates of deaths were not verified by the Swedish Death Registry (N=16). Exclusions based on dietary data included energy intake of 3 standard deviations below or above the mean, as well as substantial missing dietary data (N=793). All women with a prevalent diagnosis of cancer (excluding non-melanoma skin cancer), based on linkage with the Swedish Cancer Registry, were also excluded (N=2,403). Thus, the final study cohort comprised 61,467 women at start of follow-up.

Dietary Data

Information on diet was determined through a food frequency questionnaire included in the baseline questionnaire sent to the women. Participants were asked about intake of 67 food items commonly consumed in Sweden, with specific questions on how frequently they consumed on average an item. Respondents could choose from 8 frequency categories, ranging from never/seldom to 4 or more times per day. For bread products, respondents were also asked about

the number of slices consumed per day. Nutrients were calculated based on mean values of age-specific portions of scale-weighed foods that were recoded for 1.5 years by 213 women randomly selected from the population. Nutrient composition values obtained from the Swedish National Food Administration (NFA)[22] were used for the calculations.

Information on acrylamide levels in food items was gleaned from databases from the Swedish NFA[22] and United States Food and Drug Administration (US FDA)[23]. More than 700 food samples analyzed by the Swedish NFA and US FDA have been found to contain elevated levels of acrylamide. Estimated daily intake of acrylamide through diet was calculated based on the following food items: coffee, crisp bread, white, rye, and whole grain breads, pan fried potatoes, potato chips, French fries, biscuits, cakes, crackers, chocolate, pancakes, cereals, and meatballs. An individual's intake of each food item in grams per day was multiplied by the median concentration of acrylamide in the food item in micrograms per kilogram, and divided by 1000, and summed across all of the food items.

Colon and Rectal Cancer Cases during Follow-up

Information on incident cancer in the cohort came from the Swedish Cancer Register, established by the National Board of Health and Welfare in 1958. Swedish law mandates and regulates both physicians and pathologists to report every newly diagnosed malignant tumor from all sites to the Register.[24] As a result of this dual notification system, case reporting is essentially complete.[24] We identified through the registry 504 cancers of the colon and 237 cancers of the rectum occurring in the cohort through June 30, 2003. Dates of death in the cohort were determined through the Swedish Death Registry, while emigration from the study area was obtained by linking the cohort with the continuously updated Swedish Population Registry.

Statistical Analysis

Observation time of the cohort was calculated from date of entry into the cohort (mammography date) until the occurrence of a diagnosis of any primary colon or rectum cancer, or censoring on account of death from any cause, moving out of the study area, or end of the observation period (June 30, 2003).

The relation between dietary acrylamide and risk of colorectal cancer was assessed using time to event analyses. We assessed the risk of colon and rectal cancer separately for six food items with elevated acrylamide commonly consumed by the cohort, and for the total estimated daily acrylamide intake through diet. Proportional hazard models using Proc PHREG in SAS Version 8.2 were used to estimate the relative risk (RR) and 95% confidence interval (CI) of colorectal cancer. Quintiles of dietary acrylamide were created based on the distribution of the cohort, and modeled as categorical variables with the lowest quintile as the referent group. Tests for trend were calculated using Wald chi-square tests, where the categorical means of each quintile were modeled as ordinal variables. The following covariates collected at baseline from the questionnaire were evaluated as potential confounders: age at enrollment, years of education (categorical), body mass index (continuous), alcohol intake (categorical-quintiles), saturated fat (categorical- quintiles), dietary fiber (categorical- quintiles), and energy intake (categorical-quintiles).

The study was approved by the research Ethical Committees at Karolinska Institutet and Uppsala University, Sweden.

RESULTS:

In this cohort of 61,467 Swedish women who contributed 823,072 person-years of follow-up, 504 cases of colon cancer and 237 cases of rectal cancer occurred. The incidence rates per 100,000 person-years were 61.2 and 28.8 for colon and rectum, respectively. The mean age of the cohort at baseline was 54 years, and 42% of the women had a body mass index greater than 25 kg/m^2.

Mean intake of acrylamide through diet was 24.6 micrograms per day (interquartile range = 18.7-29.9), or 0.38 micrograms per kilogram body weight per day (interquartile range = 0.27-0.47). Less than 0.4% of women in this study consumed 1 μg/kg bw/day, a quantity often cited in risk assessment models. No cases or colon or rectal cancer occurred among the group consuming this estimated amount of acrylamide through diet.

Among the Swedish women, the major sources of acrylamide in the diet were coffee (44%), fried potato products (16%), crisp bread (15%), and other breads (12%). Women with higher acrylamide intake were more likely to be younger, have lower body mass index, and have higher levels of education than women with low acrylamide intake (Table 1). With respect to other dietary components, greater intake of acrylamide through diet was associated with increased intake of alcohol, fiber, saturated fat and total energy.

In Table 2, we examine the association between specific food items that contain acrylamide and colorectal cancer risk overall, as well as for colon and rectal cancers separately. Adjusting for potential risk factors and dietary components, we found no evidence that greater intake of coffee, crisp bread, or fried potato products was associated with a higher risk of total colorectal cancer, nor were these food items associated with colon and rectal cancers separately. There was some evidence that women who consumed greater amounts of cakes and biscuits had

a small increased risk of colorectal cancer (RR=1.4, 95% CI=1.0-1.8) and colon cancer in particular (RR=1.5, 95% CI = 1.0-2.1), but intake of these foods had no significant impact on rectal cancer (RR=1.2, 95% CI = 0.7-2.1). It is noteworthy, however, that cakes and biscuits contributed to only 6% of total dietary acrylamide.

The association between estimated dietary acrylamide intake and colorectal cancer risk is presented in Table 3. After adjusting for potential confounders, we found no evidence that estimated dietary intake was associated with cancers of the colon or rectum, or for total colorectal cancer. Comparing extreme quintiles of acrylamide intake, the multivariate adjusted relative risks (95% CI, p for trend) were for colorectal cancer 0.9 (0.7-1.3, p=0.80), for colon cancer 0.9 (0.6-1.4, p=0.83) and for rectal cancer 1.0 (0.6-1.8, p=0.77). Exclusion of cases occurring during the first two years of follow-up did not change our results. Moreover, there was no evidence of association between dietary acrylamide and risk of colorectal cancer in any subgroup defined by age at follow-up or body mass index (data available on request).

DISCUSSION:

Data from this large, population-based prospective study of Swedish women support no positive association between intake of acrylamide through dietary sources and risk of colorectal cancer. There was neither evidence of a statistical significant association nor any dose-response trend. The data also demonstrated a lack of association between specific foods that contribute most substantially to acrylamide intake, namely coffee, crisp bread and fried potatoes, and colorectal cancer risk. Given these converging data, the small increase in risk associated with higher consumption of cakes and buns is most likely due to other components of these food items.

Epidemiological studies of colorectal cancer often assess risk for both these anatomic sites combined. Yet, there appear to be differences in risk factors for colon and rectal cancer.[25] In our own study, we saw no evidence that dietary intake of acrylamide increased the risk for either cancer site. The lack of association was consistent for colon and rectal cancers.

Although this is the first prospective study of dietary acrylamide and colorectal cancer, two previous case-control studies have examined this association.[13-15] In the first published epidemiological study[13, 14], data from a population-based case control study in Sweden was reanalyzed. In addition to colorectal cancer, the authors assessed cancers of the bladder and kidney. They noted no evidence of a positive association between dietary acrylamide and any of the studied cancers. Indeed, there was a suggestion of a 40% lower risk of colorectal cancer among those with the highest intake of acrylamide. Pelucchi and colleagues[15] reanalyzed data from several large hospital-based case-control studies within Italy and Switzerland to assess the association between fried potato consumption, an important source of dietary acrylamide, in relation to cancers of the large bowel, and also oral/pharynx, oesophagus, breast and ovary**.** The

authors found no evidence of an increased risk of any cancer associated with higher fried potato consumption, and also confirmed the suggestion of a protective effect of large bowel cancer. The only other study to date examined dietary acrylamide in relation to breast cancer risk in a large cohort of Swedish women[16], and found no excess risk associated with higher intake of acrylamide.

A well-designed case-control study is an efficient design to examine the association between dietary exposure to acrylamide and cancer risk. However, this study design can be vulnerable to potential biases, including selection and recall biases. It is unlikely that the lower risk of colorectal cancer associated with dietary acrylamide in the earlier studies was due to a protective effect of acrylamide. Conceivably, this inverse association is due to chance or to changes in dietary habits after diagnosis of cancer. Although each study asked about consumption of dietary items prior to cancer diagnosis, cases might be more likely to recall their current rather than past habits.

The design of the current study avoids the possibility of recall bias. Dietary information was collected prospectively using a validated food frequency questionnaire, which reduces the likelihood of differential misclassification. Follow-up of the cohort was undertaken using national registers in Sweden, assuring virtually no loss to follow-up. The size of the cohort and number of cases were sizeable. Notwithstanding our extensive consideration of potential confounders, we cannot rule out that constituents of foods other than acrylamide, nor other risk factors, could explain this elevated risk. The baseline study questionnaire did not collect information on cigarette smoking. Thus, we could not evaluate smoking as a potential confounder, nor as an effect modifier. Data have been mixed on whether smoking is an independent risk factor for colorectal cancer [26, 27], and if anything a higher risk is restricted to

those who have smoked for several decades. Thus, it is unlikely that smoking is an important confounder of the association between acrylamide and colorectal cancer. Cigarette smoke itself is a source of exposure to acrylamide. Although we cannot evaluate the role of smoking as an effect modifier, prior studies[12, 14, 16] that have stratified on smoking have demonstrated a consistently null finding among smokers and nonsmokers.

There exists variation in acrylamide levels within and between foods[6], which could lead to nondifferential misclassification of exposure. While it appears that we can appropriately rank individuals with respect to acrylamide intake[14], we cannot rule out this bias which would in general bias estimates to the null. Finally, we have data from only one dietary assessment at baseline. Thus, if acrylamide affects cancer risk through a short-term, rather than latent effect, any changes in dietary patterns among the women over time could lead to an attenuation of the relative risk.

In light of the null findings of this and other research, an important question is why the epidemiological data on dietary acrylamide thus far seem to contradict data from animal experiments and risk assessment models? It may be that these studies are answering different questions. First, the range of exposure in animal studies is three to five orders of magnitude greater than that to which humans are generally exposed. It appears that the levels of acrylamide to which humans are exposed to in the diet may not be sufficient to increase the risk of several cancers; these studies do not preclude that substantially higher levels in humans could increase cancer risk. Second, metabolism of acrylamide in animals differs as a function of route of exposure, e.g. oral, dermal or intraperitoneal [18]. There are also large differences in metabolism rates across species[17]. Adding to the complexity, the mode of exposure between animals and humans differs, and we currently do not know about the bioavailability of acrylamide in foods.

While evidence from animal[11, 19] and risk assessment models[6, 28] suggest a small increase in risk in humans, risk assessment models have generally assumed a linear dose-response relation at low levels of exposure[29], but this is not known for certain. The level of uncertainty in these models is, indeed, substantial, being 8-9 fold difference in potential risk due to a range from a relative risk of 1.006 to 1.05 for those exposed to >1 microgram/kilogram per day.[3, 30] At the same time, researchers are reevaluating the animal data to to determine the minimum level of acrylamide in foods which could increase cancer risk. Finally, not all substances that cause tumors in rats can cause tumors in humans or even mice, because the species-specific mechanisms by which cancer occurs in rodents is not relevant to humans[29]. Epidemiological studies in general, particularly those that are prospectively designed, are valuable in addressing the role of acrylamide exposure through diet and risk of human cancer. Although such studies can never exclude a small effect of acrylamide on cancer risk, a well-designed study is able to document an effect that would be meaningful with respect to the public's health. Certainly, no single study can provide the final answer on the health effects of acrylamide in diet. However, an accumulation of evidence through well-conducted studies can shed light on this important public health concern. Our study, in combination with earlier findings, suggest that acrylamide intake in the amounts taken in through diet do not increase the risk of colorectal cancer.

ACKNOWLEDGMENTS:

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Table 1. Selected characteristics of 61,467 women in the Swedish Mammography Cohort Study at baseline 1987-1990 in relation to quintiles of estimated dietary acrylamide intake.

	Quintile of dietary acrylamide intake in 1987, μg/day				
Characteristic	Q1	Q2	Q3	Q4	Q5
Mean ± SD					
Acrylamide, μg/day	12.8 ± 3.6	20.0 ± 1.4	24.1 ± 1.2	28.6 ± 1.5	37.9 ± 8.5
Age at entry, years	57.7 ± 9.7	56.0 ± 9.6	54.0 ± 9.5	51.7 ± 9.1	49.3 ± 8.3
Body mass index in 1987, kg/m^2	25.3 ± 4.2	25.1 ± 4.1	24.7 ± 3.8	24.4 ± 3.8	24.2 ± 3.8
Alcohol intake, g/day	40.9 ± 71.1	48.4 ± 75.6	53.1 ± 76.6	60.3 ± 84.3	66.9 ± 92.6
Total energy intake, kcal	1065 ± 315	1198 ± 289	1313 ± 295	1431 ± 306	1642 ± 383
Fiber intake, g/day	14.1 ± 6.0	15.7 ± 5.6	17.1 ± 5.8	18.2 ± 5.8	20.1 ± 6.5
Saturated fat, g/day	14.9 ± 6.3	16.9 ± 6.0	18.7 ± 6.3	20.8 ± 6.7	24.5 ± 8.2
Education, % high school or above	17.3%	19.0%	19.7%	21.7%	21.7%

Table 2. Intake of selected foods with elevated acrylamide content and risk of colorectal cancer among 61,467 Swedish women, 1987-2002.

		Relative risks and 95% Confidence Intervals								
		Total Colorectal Cancer			Colon Cancer			Rectal Cancer		
Frequency of food Item	Median Acrylamide (μg/kg)*	IR†	Age Adjusted‡	Multivariate Adjusted§	IR†	Age Adjusted‡	Multivariate Adjusted§	IR†	Age Adjusted‡	Multivariate Adjusted§
Coffee	**25**									
≤ 1 cup/day		105.8	REF‖	REF‖	73.0	REF‖	REF‖	33.3	REF‖	REF‖
2-3 cups/day		90.7	0.9 (0.8-1.1)	1.0 (0.8-1.1)	61.8	0.9 (0.8-1.1)	1.0 (0.8-1.2)	30.1	1.0 (0.7-1.3)	0.9 (0.6-1.2)
≥ 4 cups/day		65.5	1.0 (0.7-1.2)	1.0 (0.7-1.3)	46.1	1.0 (0.7-1.3)	1.1 (0.8-1.5)	20.0	0.9 (0.6-1.4)	0.9 (0.6-1.4)
Crisp Bread	**138**									
≤ 1/day		86.7	REF‖	REF‖	58.1	REF‖	REF‖	29.5	REF‖	REF‖
1/day		93.4	1.0 (0.8-1.2)	1.0 (0.8-1.3)	66.7	1.1 (0.8-1.5)	1.2 (0.9-1.5)	27.0	0.9 (0.6-1.2)	0.8 (0.5-1.1)
≥2/day		84.6	0.8 (0.7-1.0)	0.9 (0.7-1.1)	53.3	0.8 (0.6-1.2)	0.9 (0.7-1.3)	33.6	1.0 (0.7-1.4)	0.8 (0.5-1.2)
Bread	**65**									
< 1/day		86.1	REF‖	REF‖	60.0	REF‖	REF‖	27.7	REF‖	REF‖
1/day		91.6	1.0 (0.9-1.2)	1.0 (0.8-1.2)	66.3	1.1 (0.9-1.3)	1.2 (0.9-1.5)	25.6	0.9 (0.6-1.2)	0.7 (0.5-1.1)
≥ 2/day		83.9	0.9 (0.7-1.1)	0.9 (0.7-1.1)	53.5	0.8 (0.6-1.0)	0.9 (0.7-1.3)	32.7	1.0 (0.7-1.5)	0.8 (0.5-1.2)
Biscuits and cakes	**100**									
Never		61.5	REF‖	REF‖	41.0	REF‖	REF‖	23.6	REF‖	REF‖
1-3 /month		85.0	1.4 (1.0-1.9)	1.5 (1.0-2.0)	67.2	1.7 (1.2-2.6)	1.8 (1.2-2.7)	17.7	0.8 (0.4-1.5)	0.9 (0.5-1.6)
1-6 /week		84.4	1.2 (0.9-1.6)	1.3 (1.0-1.7)	57.2	1.3 (0.9-1.9)	1.4 (1.0-2.0)	27.8	1.1 (0.7-1.8)	1.1 (0.7-1.8)
≥ 1/ day		107.7	1.3 (1.0-1.7)	1.4 (1.0-1.8)	72.4	1.4 (1.0-1.9)	1.5 (1.0-2.1)	37.9	1.3 (0.8-2.0)	1.2 (0.7-2.1)
Pan-fried potatoes	**292**									
Never		91.8	REF‖	REF‖	63.5	REF‖	REF‖	29.4	REF‖	REF‖
1-3/month		75.4	1.0 (0.9-1.2)	1.1 (0.9-1.3)	53.2	1.0 (0.7-1.3)	1.1 (0.9-1.4)	23.0	1.0 (0.7-1.3)	1.0 (0.7-1.4)
≥ 1/week		95.3	1.1 (0.9-1.3)	1.1 (0.9-1.4)	64.9	1.2 (0.8-1.6)	1.1 (0.9-1.4)	31.9	1.2 (0.8-1.6)	1.1 (0.8-1.6)
Potato Chips and French Fries	**450 and 1097**									
Never		101.8	REF‖	REF‖	69.1	REF‖	REF‖	33.9	REF‖	REF‖
1-3/month		47.3	0.8 (0.7-1.1)	0.9 (0.7-1.1)	33.3	0.9 (0.7-1.2)	0.9 (0.7-1.2)	14.0	0.7 (0.5-1.1)	0.7 (0.5-1.1)
≥ 1/ week		51.2	0.9 (0.6-1.4)	0.9 (0.6-1.4)	37.2	1.0 (0.6-1.7)	0.9 (0.5-1.6)	16.3	0.8 (0.4-1.8)	0.9 (0.4-2.0)

* Mean acrylamide levels in food items based on data from the Swedish National Food Administration database on acrylamide

[†] Incidence rate per 100,000 person-years
[‡] Adjusted for age at screening
[§] Adjusted for age at screening, body mass index, education, alcohol intake, energy intake, saturated fat intake, and fiber intake.
[‖] Reference category

Table 3. Estimated dietary acrylamide intake and risk of colorectal cancer among 61,467 Swedish women, 1987-2001.

	Relative risks and 95% Confidence Intervals								
	Total Colorectal Cancer			**Colon Cancer**			**Rectal Cancer**		
Quintile of acrylamide intake	IR*	Age Adjusted†	Multivariate Adjusted‡	IR*	Age Adjusted†	Multivariate Adjusted‡	IR*	Age Adjusted†	Multivariate Adjusted‡
Q1: 0-15.7 μg/day	108.1	REF§	REF§	78.7	REF§	REF§	30.0	REF§	REF§
Q2: 15.8-20.7 μg/day	106.3	1.1 (0.9-1.3)	1.1 (.9-1.4)	70.8	1.0 (0.8-1.3)	1.1 (0.8-1.4)	35.4	1.3 (0.9-1.9)	1.1 (0.7-1.6)
Q3: 20.8-25.3 μg/day	95.5	1.1 (0.9-1.4)	1.2 (0.9-1.5)	67.1	1.1 (0.8-1.4)	1.2 (0.9-1.7)	29.6	1.2 (0.8-1.9)	1.0 (0.7-1.6)
Q4: 25.4-31.4 μg/day	80.0	1.1 (0.9-1.4)	1.1 (0.8-1.4)	52.3	1.0 (0.8-1.3)	1.1 (0.8-1.5)	28.9	1.4 (1.0-2.1)	1.2 (0.8-1.9)
Q5: 31.4-307.6 μg/day	56.2	0.9 (0.7-1.2)	0.9 (0.7-1.3)	37.7	0.9 (0.6-1.2)	0.9 (0.6-1.4)	20.3	1.2 (0.8-1.9)	1.0 (0.6-1.8)
P for trend		0.80	0.85		0.48	0.83		0.31	0.77

* Incidence rate per 100,000 person-years
† Data adjusted for age at screening.
‡ Data adjusted for age at screening, body mass index, education, alcohol intake, energy intake, saturated fat intake, and fiber intake.
§ Reference category