Assessing the Human Intake of Heterocyclic Amines: Limited Loss of Information Using Reduced Sets of Questions[1]

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Abstract

The aim of this study was to evaluate loss of information from a reduced food frequency questionnaire as compared with an extensive reference method developed to assess the intake of heterocyclic amines (HCAs). Food frequency data were linked to concentrations of HCAs in cooked foods to estimate the individual daily exposure to a combination of five HCAs. The number of food items in the questionnaire was reduced and selected in three ways: (*a*) according to the contribution to the estimated total intake; (*b*) the between-person variance; or (*c*) dishes included in other studies. The effect on sensitivity, specificity, concordance, the correlation coefficient, κ, and simulated relative risks was determined using information from a population-based study conducted in Stockholm. Only a limited amount of misclassification was introduced when the number of dishes was reduced from 39 to 15 or 20, and no major difference was seen when dishes were selected according to the total intake or the between-person variance. Our data indicate that for a specific exposure, such as HCAs, the loss of accuracy in an analytical epidemiological study is small and may not be relevant when the number of dishes in a food frequency questionnaire is decreased, if the initially chosen dishes are carefully selected and cover a reasonable part of the total intake or between-person variance.

Introduction

High consumption of meat has been associated with an increased risk of colorectal cancer (1–5). Such a risk may be due to substances naturally occurring in the meat *per se*, agents added to the meat, or compounds formed during cooking. Mutagenic HCAs[4] are formed from amino acids, creatine/creatinine, and sugar (6, 7) and were first measured in the charred parts of cooked meat and fish (8). To assess the intake of HCAs, factors to be considered include not only the type of dish ingested, portion size, and frequency of consumption but also cooking methods, cooking temperature, intake of gravy, and the concentration of HCAs in each dish.

The validity of an observational study assessing the cancer risk of any food item, including HCAs, can be distorted by confounding and bias arising from nonparticipation and measuring errors (9, 10). The extent of misclassification depends on the sensitivity and specificity of the dietary assessment method. In epidemiological research, the trade-off between an extensive, accurate, and time-consuming method for a shorter version is often guided by practical and financial considerations. When reducing the number of items in a questionnaire, identifying a method to select the most informative food items may reduce the resulting systematic error. The magnitude of misclassification introduced when making these compromises and the effect on risk estimates must be considered for different reduction methods.

There are alternative means of identifying informative food items to design reduced sets of questions. One may choose food items that contribute most to the total intake of the nutrient of interest in the study population, or one may select food items that vary most between subjects. The latter way is thought to be an effective method when the aim is to rank people according to their intake and when the absolute level of intake is of less importance, as is often the case in epidemiological analytical studies (11).

In a Swedish population-based study, the intake of HCAs was estimated by linking consumption data collected by means of an extensive food frequency questionnaire to concentrations of HCAs in cooked meat and fish dishes (12). In the present analysis, we simulated three different reduced sets of questions and assessed the degree of misclassification as compared to the original questionnaire. In addition, to elucidate the effect on risk estimates, we simulated RRs using the reduced sets of questions.

Patients and Methods

Study Population. In this study, data were used from a previously conducted case-control study on exposure to food mutagens and cancer risk (13). Subjects were born in Sweden between 1918 and 1942 and had a permanent address in a demarcated geographical region in and around Stockholm for at

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[4] The abbreviations used are: HCA, heterocyclic amine; ICD, International Classification of Disease; RR, relative risk; IQ, 2-amino-3-methylimidazo[4,5-f]quinoline; MeIQ, 2-amino-3,4-dimethylimidazo[4,5-f]quinoline; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine.

least 1 month during the observation period from November 1, 1992 to December 31, 1994. Information about cases was retrieved from the population-based cancer registry in Stockholm. Notification to the registry is mandatory by law for both attending physicians and pathologists. Controls were randomly selected from a population registry during the observation period and frequency-matched according to age (5-year intervals) and gender distribution among the cases of colon cancer.

A questionnaire was mailed to the subjects after they had received an introductory letter. After returning the questionnaire, missing information was completed by telephone interviews. Altogether, information was retrieved from 548 controls and 1056 cases of cancer of the colon (ICD 153), rectum (ICD 154), bladder (ICD 188), or kidney (ICD 189) according to the International Classification of Diseases, Injuries and Causes of Death (14). The response rate was 80% for controls and 70% for cases.

The Referent Dietary Assessment Method. The extensive dietary assessment method is described in detail elsewhere (12). In brief, diet was assessed by means of a semiquantitative food frequency questionnaire including a total of 188 food items, including 27 fried meat dishes, 16 oven-roasted meat dishes, 11 boiled meat dishes, 4 grilled meat dishes, 7 fish dishes, 2 egg dishes, and 1 blood pudding, as well as 4 different types of gravy/sauce. All questions took account of eating habits five years previously. Ten categories of intake frequencies ranged from “2–3 times/day” to “never.”

Variables used to assess the intake of HCAs from meat and fish were type of meat/fish ingested, frequency of consumption, portion size, cooking method, degree of surface browning, and concentration of HCAs. Color photos showed six dishes, each fried at four different temperatures, giving varying degrees of surface browning. Each photo corresponded to a known frying temperature.

To assess concentrations of HCAs, 22 cooked dishes with pan residues were analyzed (15 fried meat dishes, 3 baked/roasted meat dishes, 2 fried fish dishes, 1 fried egg dish, and 1 blood pudding). Nineteen dishes were fried in a standardized manner at 150°C, 175°C, 200°C, and 225°C, and three were roasted/baked in a normal household oven at 150°C and 200°C. Chemical analyses and the obtained concentrations of HCAs (IQ, MeIQ, MeIQx, DiMeIQx, and PhIP) in the cooked foods have been reported in detail elsewhere (15–17). For the remaining fried dishes in the questionnaire, the classification of surface browning and concentration of HCAs were derived from the 6 photographed dishes and the 22 analyzed dishes, respectively (12).

The intake of HCAs from pan residue and gravy was calculated using a method described previously (12) that gives the concentration in one individually calculated standard serving.

The Reduced Dietary Assessment Methods. To reduce the set of questions on the frequency of intake of fried/baked/grilled dishes, we computed the mean contribution of each dish to the total intake of HCAs among controls. After this, sets of informative dishes were generated using three alternative principles. First, all meat and fish dishes were ordered according to their contribution to the total mean daily intake of HCAs (18). This ranking was done for the meat/fish dishes and the corresponding gravy, both separately and combined. Secondly, the dishes were ordered according to their contribution to the between-person variance, using a stepwise regression (11). Thirdly, groupings of dishes of special interest were formed, *i.e.*, dishes used in another Swedish study (the 6 photographed dishes) and in Dutch studies (a set of 18 dishes that approximate habitual meat dishes in the Netherlands and are part of a 22-dish questionnaire used in a case-control study on dietary factors and colorectal adenomas).

Data Analysis. To explore misclassification by the reduced sets of questions, controls and cases were categorized into quintiles based on the distribution of the intake of HCAs in controls. The ability of the reduced sets of questions to categorize subjects into the same quintile as the reference method was estimated separately in terms of sensitivity and specificity for each quintile. Sensitivity is defined as the probability of a positive test result (*e.g.*, quintile 1 according to the reduced method), provided the exposure is truly present (*i.e.*, quintile 1 according to the reference method). Analogously, specificity is the proportion of truly nonexposed subjects (*e.g.*, quintiles 2–5 according to the reference method) who are correctly categorized as nonexposed by the test (*i.e.*, the same quintiles according to the reduced method). Furthermore, Pearson correlation coefficients for quintiles were calculated, as well as κ, a measure of concordance in contingency tables, taking into account agreement on the basis of chance alone (11).

To explore the effect of misclassification on the range of RRs that may be anticipated in epidemiological studies, RRs of magnitude $RR = 2$ and $RR = 3$ were simulated. Using the reference method, the exposure to HCAs was categorized into quintiles based on the distribution among controls, resulting in equal numbers of controls in each category of intake. The case distribution over the quintiles was selected to simulate “true” RRs of 2.0 and 3.0 for the highest *versus* the lowest quintile of intake. These selected cases and all controls were subsequently categorized into new quintiles based on the distribution of the intake of HCAs, using the reduced methods. Logistic regression (19) was used to model the odds ratio, estimating the incidence rate ratio (RR) between the exposed and unexposed members of the study population.

Results

Table 1 shows the mean amount of HCAs (IQ, MeIQ, MeIQx, DiMeIQx, and PhIP) contributed by each dish to the total mean intake among controls. Considering the contribution stemming from meat and gravy combined, the 10 dishes contributing the most were fried bacon, minced-beef patties (*i.e.*, hamburgers), pork filet, chicken/turkey, meatballs, pork belly, loin of pork, entrecote (*i.e.*, beef steak) and (minced) meat sauce. These dishes contributed 77% of the total intake of HCAs among controls as obtained using the extensive method. The top 15 and 20 dishes contributed 88% and 94% of the total intake, respectively. The remaining 6% of the intake was generated by an additional 20 dishes. The total mean intake of HCAs from all 39 meat and fish dishes was 157 ng/day. MeIQx and PhIP each comprised of 45%, DiMeIQx comprised 10%, and IQ and MeIQ both comprised less than 1% of the total intake of HCAs (data not shown).

In this population, gravy is very often prepared from pan residues and eaten with most meat dishes. Therefore, gravy contributes substantially to the total intake of HCAs. The dishes contributing the most were minced beef patties, pork filet, loin of pork, pork chops, entrecote, meat stew, beef steak, and, finally, pork belly.

When ranking the top 10 dishes according to the explained percentage of the between-person variance in the total intake (Table 2), 9 of 10 dishes were the same as when ranked according to the total intake, but the dishes appeared in a different order.

Table 1 Contribution of meat and fish dishes and gravy to the total intake of HCAs in an elderly population in Stockholm

Dish no.	Meat dish	Meat intake		Gravy intake		Total intake		
		ng	% meat	ng	% gravy	ng	% total	% cumulative
1	Bacon, fried	26.1	24.6	0.5	1.0	26.6	16.9	16.9
2	Minced beef patties, fried	6.8	6.5	10.4	20.4	17.3	11.0	27.9
3	Pork fillet, fried	5.3	5.0	7.1	13.9	12.4	7.9	35.8
4	Chicken/turkey, fried	11.1	10.5	0.5	1.0	11.6	7.4	43.2
5	Meatballs, fried	8.8	8.3	2.3	4.5	11.1	7.1	50.3
6	Pork belly, fried	8.9	8.3	1.5	2.9	10.3	6.6	56.8
7	Loin of pork, fried	4.1	3.9	6.0	11.8	10.1	6.4	63.3
8	Pork chops, fried	4.9	4.6	5.2	10.2	10.1	6.4	69.7
9	Entrecote, fried	3.9	3.7	3.1	6.1	7.0	4.4	74.1
10	Minced meat sauce	5.3	5.0	0.0	0.0	5.3	3.3	77.5
11	Beef steak, fried	2.9	2.7	2.2	4.3	5.1	3.2	80.7
12	Beef fillet, fried	2.1	1.9	1.6	3.1	3.6	2.3	83.0
13	Smoked pork, fried	1.5	1.4	1.3	2.5	2.7	1.7	84.8
14	Stew, browned	1.1	1.0	1.6	3.1	2.7	1.7	86.5
15	Fish, fried (breaded)	2.2	2.0	0.2	0.4	2.4	1.5	88.0
16	Lamb, fried	1.8	1.7	0.3	0.6	2.1	1.3	89.4
17	Minute beef, fried	0.9	0.8	1.1	2.2	1.9	1.2	90.6
18	Game, fried	1.2	1.1	0.6	1.2	1.8	1.1	91.8
19	Beef, grilled	1.2	1.1	0.6	1.2	1.8	1.1	92.9
20	Ham, fried	0.7	0.7	0.9	1.8	1.6	1.0	93.9
21	Pork stew, browned	0.6	0.5	0.9	1.7	1.4	0.9	94.8
22	Pork, grilled	0.7	0.7	0.5	1.0	1.2	0.8	95.6
23	Minced meat dish, grilled	0.6	0.5	0.4	0.8	1.0	0.6	96.3
24	Meat loaf, roasted	0.9	0.9	0.0	0.1	1.0	0.6	96.9
25	Black pudding, fried	0.8	0.8	0.0	0.0	0.8	0.5	97.4
26	Beef patties, roasted	0.3	0.3	0.5	1.0	0.8	0.5	97.9
27	Meat balls, roasted	0.6	0.5	0.1	0.2	0.7	0.4	98.4
28	"Falu" sausage, fried	0.0	0.0	0.5	1.0	0.5	0.3	98.7
29	Fish sticks, fried	0.4	0.4	0.1	0.1	0.5	0.3	99.0
30	Chicken/turkey, roasted	0.1	0.1	0.4	0.8	0.5	0.3	99.3
31	"Wiener" sausage, fried	0.0	0.0	0.2	0.4	0.2	0.1	99.5
32	"Chipolata" sausage, fried	0.2	0.2	0.0	0.0	0.2	0.1	99.6
33	Smoked sausage, fried	0.0	0.0	0.2	0.3	0.2	0.1	99.7
34	Fish, fried (not breaded)	0.2	0.2	0.0	0.0	0.2	0.1	99.8
35	"Stång" sausage, fried	0.0	0.0	0.1	0.2	0.1	0.1	99.9
36	Sausage, grilled	0.0	0.0	0.0	0.1	0.1	0.0	100.0
37	Sausage, fried	0.0	0.0	0.1	0.1	0.1	0.0	100.0
38	"Falu" sausage, roasted	0.0	0.0	0.0	0.0	0.0	0.0	100.0
39	"Wiener" sausage, roasted	0.0	0.0	0.0	0.0	0.0	0.0	100.0
Total		106.2		50.9		157.1		

Table 2 Ranking of most informative dishes according to between-person variance in intake of HCAs using stepwise regression analysis

Dish no.	Meat dish	Cumulative R^2	CC[a]	Cumulative % of total intake
1	Pork chops, fried	0.48	0.70	6.4
2	Bacon, fried	0.70	0.63	23.3
3	Minced beef patties, fried	0.83	0.60	34.3
4	Entrecote, fried	0.89	0.35	38.7
5	Loin of pork, fried	0.93	0.44	45.1
6	Pork belly, fried	0.94	0.56	51.7
7	Pork fillet, fried	0.96	0.60	59.6
8	Chicken, fried	0.97	0.22	67.0
9	Fish, fried (breaded)	0.98	0.22	68.5
10	Minced meat sauce	0.98	0.39	71.8

[a] CC, simple Pearson coefficient of correlation for each dish to the total daily intake.

Considering the contribution from both meat and gravy, the 10 dishes contributing the most, in descending order, were fried pork chops, bacon, minced beef patties, entrecote, loin of pork, pork belly, pork filet, chicken, breaded fish, and (minced) meat sauce. These dishes accounted for 98% of the variance and 72% of the total intake of HCAs. A daily mean intake of HCAs based on these dishes would be 113 ng. The cumulative R^2 (percentage of the between-person variance) and the percentage of the daily intake of HCAs accounted for by varying numbers of dishes, as selected by these two principles, are shown in Fig. 1.

Sensitivity and specificity for different reduced sets of questions compared to the reference method are shown in Table 3. For sets of questions including 20 and 15 dishes, sensitivity and specificity were equally good, regardless of the selection principles. A reduced questionnaire including 10 dishes performed less well, but the sensitivity was somewhat better for dishes selected according to their contribution to the total intake than for dishes selected according to variance. When only five dishes were used, the reduced methods performed even worse, and again, sensitivity was better for dishes selected according to contribution to the total intake than for dishes selected according to the amount of between-person variance.

Concordance was measured as the ability of a reduced set of questions to categorize each person into the same quintile as

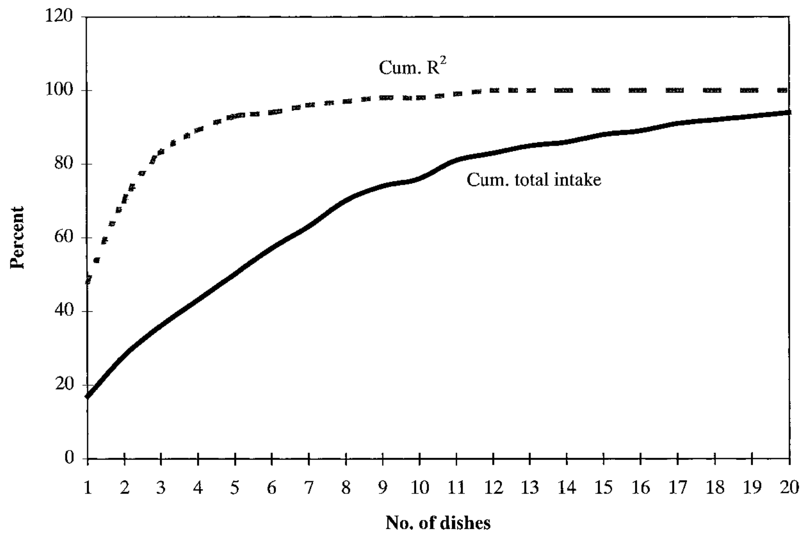

Fig. 1. The cumulative percentage of the between-person variance (R^2) and the percentage of the daily intake of HCAs accounted for by varying the numbers of dishes included in the reference method.

Table 3 Performance of truncated methods compared to the reference method by quintile (Q) of exposure

Truncated methods	No. of dishes	Sensitivity (%)					Specificity (%)					Concordance[a]			r^b	κ^c
		Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5	% same Q	% 1Q off	% > 1Q off		
Total intake																
	5	82	67	68	65	86	97	91	89	94	96	74	26	1	0.92	0.67
	10	88	85	78	85	93	99	94	95	96	98	86	14	0	0.96	0.82
	15	90	90	88	92	96	99	96	97	98	99	91	8	0	0.98	0.89
	20	94	93	95	95	98	100	98	98	99	100	95	5	0	0.99	0.94
Between-person variance																
	5	72	51	59	60	85	95	88	86	92	96	65	33	2	0.89	0.57
	10	85	76	70	80	93	98	93	93	94	98	81	19	0	0.94	0.76
	15	88	88	88	91	95	99	95	96	97	99	90	10	0	0.98	0.87
	20	92	91	91	96	97	99	97	98	98	100	93	7	0	0.98	0.92
Swedish method	6	74	49	50	58	79	96	88	85	88	95	62	34	3	0.87	0.52
Dutch method	18	90	90	86	90	97	99	96	97	98	99	90	9	0	0.97	0.88

[a] The percentage of subjects categorized on the basis of a reduced method in the same quintile (% same Q), one quintile higher or lower (% 1Q off), and more than one quintile away from the same quintile (% > 1Q off).
[b] Pearsons coefficient of correlation for categorization into quintiles.
[c] κ is a measure of concordance taking chance into account $(p^o - p^e)/(1 - p^e)$.

the reference method. The concordance increased rapidly from 5 to 15 dishes; however, only small improvements were seen for a total of 20 dishes. Dishes selected according to the total intake generally performed better than dishes chosen by variance. The Pearson correlation coefficient increased with an increasing number of dishes but performed equally well in the two methods of selecting dishes. κ, a measure of concordance accounting for chance, increased rapidly with the number of dishes, but dishes selected according to the total intake gave higher values.

The sensitivity and specificity of the "Dutch module" including 18 dishes were higher than 0.85 in all quintiles. More than 90% of the subjects were classified into the same quintile as when using the reference method, 9% were classified one quintile higher or lower than in the reference method, and none were classified more than one quintile higher or lower than in the reference method. The correlation between the Dutch module and the reference method was also high. The short Swedish method comprising six dishes performed less well.

The effect of decreased sensitivity and specificity on the estimated relative risks is shown in Table 4. Only small effects on the RRs were seen for the reduced methods comprising 10, 15, or 20 dishes, regardless of the selection criteria. RRs based on truncated modules comprising only five dishes deviated markedly from the simulated "true" RRs, especially for the five dishes selected according to the between-person variance.

Discussion

We studied the loss of information when reducing an extensive food frequency questionnaire designed to estimate human intake of HCAs as part of a population-based study of cancer risk. The findings of this study indicate that the loss of information is limited when the number of enumerated dishes was reduced from 39 to 15 or 20. Results were similar for the two principles of selection when using 15 or 20 dishes. Using 5 or 10 dishes, estimates of intake based on dishes selected according to the total intake of HCAs were more accurate than those based on dishes selected according to the between-person variance.

The reference method in this study was an extensive semiquantitative food frequency questionnaire designed to estimate human cancer risks as related to HCAs in a Swedish

Table 4 The effect of misclassification by truncated methods on RR estimates for each quintile (Q) of exposure

Methods	No. of dishes	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
Simulated true RR	39	1.00	1.24	1.50	1.72	2.00	1.00	1.50	2.02	2.48	3.03
Total intake	5	1.00	1.41	1.85	1.62	2.15	1.00	1.49	2.35	2.22	3.02
	10	1.00	1.57	1.64	1.96	2.22	1.00	1.84	2.12	2.83	3.26
	15	1.00	1.49	1.74	2.00	2.18	1.00	1.72	2.30	2.87	3.25
	20	1.00	1.30	1.68	1.83	2.06	1.00	1.47	2.19	2.56	3.02
Between-person variance	5	1.00	1.34	2.11	1.67	2.20	1.00	1.52	2.68	2.25	3.14
	10	1.00	1.40	1.56	1.84	2.14	1.00	1.56	1.99	2.43	3.04
	15	1.00	1.52	1.62	1.93	2.13	1.00	1.83	2.12	2.74	3.18
	20	1.00	1.32	1.50	1.95	2.00	1.00	1.55	1.97	2.75	2.97
Swedish method	6	1.00	1.45	2.08	1.95	2.33	1.00	1.61	2.70	2.61	3.33
Dutch method	18	1.00	1.50	1.47	1.89	2.18	1.00	1.81	1.95	2.72	3.29

population (12). The selection of dishes was based on previous studies of frequently eaten fried foods in an elderly population in Stockholm. The total intake of HCAs was estimated using questionnaire data on the cooking method, frying temperature, portion size, intake frequency, and intake of gravy and data on the concentration of HCAs in various dishes from chemical analyses. The extensive food frequency questionnaire was used as a reference method but cannot be considered a gold standard. Validation of HCA intake by identifying DNA adducts (20–23), excretion of HCAs in urine (24), or collecting double portions of food for chemical analysis (11) may be possible. However, these approaches have their own methodological and analytical limitations.

To compose a database of HCA content in cooked meat, 22 dishes and corresponding gravies were cooked in a standardized manner at different temperatures, resulting in 152 samples. Subsequently these dishes were chemically analyzed for the five HCAs, IQ, MeIQ, MeIQx, DiMeIQx, and PhIP. If the chemical analysis of these samples suffered from systematic errors, this would result in a systematic shift in the magnitude of the estimated HCA intake in both cases and controls. However, random analytical errors may result in nondifferential misclassification, diluting the association and therefore increasing the chance of missing a possible real carcinogenic effect of HCAs (β-error).

Of a total of 39 dishes in the questionnaire, the 22 analyzed dishes account for 79% of the total intake of HCAs among controls as estimated using the reference method. The remaining 17 dishes were not cooked and analyzed, but data on HCA content were taken from similar dishes (12), which may have introduced some additional measurement errors. Considering the large number of dishes cooked and analyzed, the magnitude of these errors is probably relatively small.

As shown by others (18, 25), using the percentage contribution to the total intake or using the percentage explained of the between-person variance derived by stepwise regression is a legitimate method to reduce the number of items in a questionnaire. Of course, subjects may respond differently to *n* items in an extensive 188-item questionnaire than to a short questionnaire including the *n* items only. It is difficult to argue which of those approaches would lead to the most valid estimate.

In this study, the reduced methods biased some of the true RRs upward, instead of toward the null. This may be caused by the fact that a continuous variable is categorized into five categories, which is known to sometimes result in a bias away from the null (26, 27). Furthermore, the selection of dishes is based on the controls, which may lead to some bias if patterns of consumption of meat dishes are substantially different in cases.

When studying the effect of exposure to HCAs on cancer risk, one should study individual HCAs because they occur in varying concentrations in different foods (28–30) and may have different mutagenic and carcinogenic effects. To facilitate the methodological aims of this study, we summed the intake of five HCAs to estimate total intake. However, when a specific HCA is the relevant exposure in studies of cancer risk, an estimation of the total intake of HCAs would be a suboptimal surrogate variable, especially if the amine occurs in relatively low concentrations compared to the other HCAs. Indeed, intake of individual HCAs may be better estimated by different sets of dishes, as was recently shown by Byrne *et al.* (31). The methods described here can be used to assess which dishes to include in a relatively short questionnaire and what the effect on misclassification may be.

In conclusion, a limited amount of misclassification was introduced when the number of fried/baked/grilled meat and fish dishes was reduced. This may imply that food frequency questionnaires focused on intake of HCAs can be relatively short. One reason to shorten a questionnaire is to increase the participation rate, which may improve the accuracy of the findings more than the decrease introduced by the additional measurement error.

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