COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Consumption of Alcohol and Pancreatic Cancer Risk

1. As part of the strategy proposed to consider the role of alcohol consumption and cancer risk, it was suggested that the COC review the epidemiological data on alcohol consumption and cancer. In 2007 (published IARC, 2010), IARC reviewed the epidemiological evidence on the possible association between alcoholic beverage consumption and cancer at 27 anatomical sites (cancers of the oral cavity and the pharynx, larynx, oesophagus, liver, breast, stomach, colon and/or rectum, pancreas, lung, urinary bladder, endometrium, ovary, uterine cervix, prostate, kidney, lymphatic and haematopoietic system, testis, brain, thyroid, melanoma and other female cancers (vulva and vagina)). They re-affirmed their previous conclusion (IARC, 1988) that cancers of the upper digestive tract (oral cavity, pharynx, larynx, oesophagus) and the liver are causally related to the consumption of alcoholic beverages. In addition, IARC considered that there is sufficient evidence to conclude that cancer of the colorectum and female breast are causally related to the consumption of alcoholic beverages (IARC, 2007). Following another IARC review in 2009 (IARC, 2012), IARC reaffirmed their position for the aforementioned cancers and also reported an association between alcohol consumption and cancer of the pancreas, although they were unable to reach a conclusion on whether this was causal.

2. In view of the recent IARC evaluation, Members agreed that an update review of the epidemiological literature on alcohol consumption and all the cancer sites was not necessary at this time. However, members agreed that a review of the epidemiological literature published since the IARC review in 2009 on alcohol consumption and pancreatic cancer might provide insight into whether pancreatic cancer is causally related to alcohol consumption. This review considers epidemiological studies (pooled/meta-analysis, cohort and case-control studies) published since the last IARC review.

Pancreatic Cancer Statistics for the UK

3. Pancreatic cancer was the 10th most common cancer in the UK in 2010 (Cancer Research UK), accounting for 2.6% of all cancers. It was the 12th most common cancer in men and 8th most common cancer in women in the UK, with around 4,200 men and 4,300 women diagnosed with pancreatic cancer in 2010 giving a male:female ratio of almost 1:1. The overall incidence rate in the UK was 9.4 cases in 100,000 people (9.4/100,000), with incidence rates of 10.6/100,000 in men and 8.4/100,000 in women. Around 8 out of 10 pancreatic cancer cases occurred in people aged 60 and over. Pancreatic cancer rates for men declined slightly between the late 1970s and mid-1990s, and since then have remained stable. Pancreatic cancer rates for women declined between the late 1980s and late 1990s, but since then have gradually increased. Pancreatic cancer was the fifth most common cause

of cancer death in the UK; around 8,300 people in the UK died from pancreatic cancer in 2011 (mortality rate of 9.0/100,000 per population). In 2010, the lifetime risk of developing pancreatic cancer in the UK was estimated to be 1 in 73 for men and 1 in 74 for women (Cancer Research Statistical Team, 2012).

Pancreatic Cancer Risk Factors

4. Parkin et al. (2011) estimated that, in the UK, around 36% of pancreatic cancers in men and 39% in women are linked to lifestyle factors. Smoking is a major risk factor for pancreatic cancer and Parkin (2011) estimated that around 29% of pancreatic cancers in the UK in 2010 were caused by smoking. Other risk factors for pancreatic cancer identified from the literature include genetic factors, background diseases, bodyweight and physical activity, family history, diet, and certain drugs. Alcohol consumption has also been identified as a risk factor but its exact role is unclear.

Alcohol Consumption

5. Previously, the PHE Toxicology Unit provided members with a paper (CC/2013/13) on the estimates of alcohol consumption, types of alcohol consumed and trends and habits of alcoholic beverage consumption in the UK, Europe and globally. In brief, the paper provided data on the total alcohol consumption worldwide and in the EU and demonstrated the wide variation in the volume of alcohol consumed across countries. In the UK, alcohol consumption in adults has increased over the past thirty years; however, there has been a downward trend since the peak of 2004. Men continue to consume more alcohol than women. The frequency of consumption increases with age. Younger people are more likely to drink heavily on a single occasion. There has been an overall reduction in the numbers of 11-15 year olds drinking alcohol and the amount they consumed in recent years. Information was also provided on the frequency of alcohol consumption and the maximum amount consumed in a day in the UK. This information gave a clear indication of the proportion of the population that are drinking above the government's recommended daily limits.

Alcohol consumption and pancreatic cancer

6. Alcohol consumption as a factor in pancreatic cancer remains uncertain. In earlier cohort and case-control studies and those considered in the IARC monograph (96 2010, annex A) on alcohol, IARC found limited association between the consumption of alcoholic beverages and the risk of pancreatic cancer. At the time IARC concluded that there was not strong evidence for an association. However, when IARC considered this again, including a number of additional studies (IARC 2012, monograph 100E, annex B), it was concluded that there was an association between alcohol consumption and cancer of the pancreas, although causality could not be established. Literature for this review was obtained following a Pubmed search and the search terms included alcohol, ethanol, drinking, consumption, pancreas and pancreatic cancer. Studies published since January 2008 to January 2014 were included in the retrieval to ensure all studies published on this topic since the last IARC review to date were included.

Meta- and Pooled analyses

7. Two pooled analyses and one meta-analysis have been performed since the last IARC review (Table 1). The first pooled analysis comprised of 12 cohort studies in the PanScan (Michaud et al., 2010) and the second of 10 case-control studies from the PanC4 (Lucenteforte et al. 2012). The meta-analysis comprised of five case-control studies (Li et al, 2011).

8. The pooled analysis of Michaud et al. (2010) involved a total of 1,530 cases and 1,530 controls from the PanScan nested case-control study. The analysis was conducted in both men and women and the odds ratio (OR) and 95% confidence intervals (95% CI) were calculated using the unconditional logistic regression and were adjusted for either a) age, cohort, and sex or b) age, cohort, race, smoking status, diabetes and BMI. Exposure assessment of alcohol consumption varied between the studies. Some studies expressed alcohol consumption in terms of grams of ethanol consumed per day. In order to have a uniform variable of alcohol consumption for the pooled analysis, the authors calculated the amount of alcohol consumed in terms of grams of ethanol for each alcoholic beverage type for those studies which did not provide intake in grams of ethanol per day. The reference group in the analyses of total alcohol intake and pancreatic cancer was the group that consumed >0 to < 5 g/day and in the alcohol specific type analyses it was the non-drinking group (0g/day). Michaud et al. (2010) reported that seven of the 10 studies reported positive associations for total alcohol intake and pancreatic cancer risk with the studies with smaller numbers tending to show stronger associations. The pooled OR was slightly higher in non-drinkers (OR= 1.19, 95% CI 0.97 – 1.48) compared to drinkers of <5 g/day (referent group) and there was no clear association found in the combined analysis of men and women up to 30 g/day. An association was observed at the higher total alcohol intake groups (for example > 60g/day (OR= 1.38, 95% CI 0.86 – 2.23), but this was not statistically significant. The pooled analysis for total alcohol intake comparing those that consumed over 30g/day to those who consumed between >0 and <10g/day was not statistically significant (OR =1.23, CI 95% 0.97 – 1.57). In their analyses of alcoholic beverage type, Michaud et al. (2010) found a statistically significant increase in pancreatic cancer risk in men consuming ≥ 45g/day of liquor (spirits) compared to non-drinkers (OR=2.23, 95% CI 1.02 – 4.87). This association was not statistically significant in women or in men and women combined. No associations were observed for wine or beer. Michaud et al. also examined alcohol intake by smoking status but did not observe a statistically significant interaction between alcohol consumption and smoking.

9. Lucenteforte et al. (2012) performed a pooled analysis on 10 case-control studies from the PanC4 consortium. This analysis was larger than the Michaud et al. analysis and included 5,585 cases and 11,827 controls. The ORs and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression and were adjusted for age, cohort, sex, education, race, smoking status, diabetes history and BMI. Exposure assessment of alcohol consumption varied between the 10 studies. In order to create a uniform variable for alcohol consumption across all the studies, Lucenteforte et al. converted the beverage volume of each alcoholic beverage specified in the questionnaires into milliliters. The reference group in the analysis of total alcohol intake and pancreatic cancer was the group that consumed 0 to <1 drinks/day. When they compared abstainers or occasional drinkers (<1

drink/day), risk estimates were near unity for < 4 drinks per day (OR = 0.93; 95% CI 0.69 – 1.26) and above unity for individuals who consumed ≥ 9 drinkers per day (OR = 1.6, 1.2 - 2.2) but this was not statistically significant. In an analysis by alcohol beverage type, ORs were increased for subjects drinking ≥ 4 drinks of wine/day (OR = 1.5, 95% CI 1.0 – 2.1) but no increased risk was observed for consumption of beer or liquor, although the authors suggest that was because the data was sparse. The authors demonstrated the pooled ORs for pancreatic cancer with total alcohol consumption using a forest plot and they observed that the ORs were elevated for the highest category of alcohol consumption in 6 of the 10 studies. The pooled OR was 0.9 (95% CI 0.7–1.2) for 1 to <4 drinks per day, 1.2 (95% CI 1.0–1.5) for 4 to <6 drinks per day, and 1.5 (95% CI 1.2–1.8) for ≥6 drinks per day. They did not observe any significant differences in the risk estimates when the results were stratified by smoking (ever, former, and current smokers).

10. Li et al. (2011) carried out a systematic review on both cohort and case-control studies and a meta-analysis on case-control studies investigating the association between alcohol consumption and cancer risk including pancreatic cancer in the Chinese population. The meta-analysis was performed using the random effects model.1612 cases and 3997 controls were included in the analysis of pancreatic cancer. In their combined analysis of men and women, comparing non-drinkers with drinkers, Li et al. observed little of no effect of alcohol consumption on pancreatic cancer risk (OR= 1.15, 0.97 -1.37). In their subgroup analyses, they observed an association between alcohol consumption and pancreatic cancer in men (OR= 1.71 99% CI 1.32-2.20) but not in women (OR=1.16, 99% CI 0.52 – 2.60).

Cohort studies in the General Population

11. In addition to the cohort studies included in the pooled analysis above, a number of recent cohort studies have examined the association between alcohol consumption and pancreatic cancer, Wang et al (2011), Kuzimickiene et al. (2013), Stevens et al. (2009), Nakamura et al. (2011), Gapstur et al. (2011) and Anderson et al. (2012) have all considered the role of alcohol consumption as a risk factor for pancreatic cancer (Table 2).

12. Wang et al. (2011) examined the effect of several pancreatic cancer risk factors (including alcohol consumption) on patient survival in a cohort of 488 patients with histologically confirmed pancreatic cancer in the Guangzhou Province in China. The study population were followed from 1998 to 2010. Information on the lifestyle factors for each patient were collected by the clinical staff. Overall survival (OS) and Hazard ratios were calculated from the date of diagnosis to the date of patient death from cancer or the last date of follow-up. In their univariate analysis determined by Cox regression, alcohol consumption was not association with overall survival from pancreatic cancer (1.16, 0.91 – 1.47).

13. Kuzimickiene et al. (2013) investigated the association between different lifestyle factors and the risk of pancreatic cancer in a prospective-based cohort study of 7132 men in Lithuania with up to 30 years of follow-up. Information on alcohol consumption was obtained by interview. Hazard ratios (HR) and 95% CI were estimated using Cox proportional hazard regression models. They identified 77 cases of pancreatic cancer in the follow up. Frequent alcohol consumption was

associated with a non-statistically significant higher risk of pancreatic cancer. The HZ among men who consumed alcohol the most frequently (2-7 times per week) was 1.79 (95% CI 0.64 – 5.00) compared to men who drank occasionally (a few times a year). In their analysis by total alcohol intake, they found that men consuming ≥100.0g/week of ethanol had a HR of 1.57 95% CI 0.66 – 3.74 compared to men consuming 0.1 – 9.9 g/week. The study suggests that there is an elevated risk of pancreatic cancer among men with the highest alcohol consumption frequency and quantity.

14. Stevens et al. (2009) examined the association of demographic and lifestyle factors with pancreatic cancer in a prospective cohort study of 1.3 million middle-aged women in the UK, recruited from 1996 to 2001. Information on each participant's lifestyle such as smoking and drinking habits was obtained by questionnaire. Relative risks (RR) and 95% CI were estimated using Cox proportional hazard models and adjusted for age, region, socioeconomic status, smoking, body mass index and height. During the follow-up period, there were 1,338 cases and 1,710 deaths from pancreatic cancer (note that follow up for mortality was longer than the follow up for incidence). Examining the incidence data, they found that the risk of pancreatic cancer did not vary significantly with increasing alcohol consumption (RRs = 1.07, 1.00, 0.88, 1.00, 1.08 for non-drinker, 1-2 units per week as the referent group, 3 – 6 units per week, 7 – 13 units per week, and 14 + units per week, respectively). The study reported that current smokers at recruitment were at increased risk of pancreatic cancer compared to never smokers (RR= 2.39, 95% CI 2.10 – 2.73) and these RR's did not vary with alcohol consumption.

15. Nakamura et al. (2011) examined the association between smoking and lifestyle factors including alcohol consumption in a population-based prospective cohort design study of 30,826 participants (14241 men and 16585 women) in Takayama, Japan. The study took place from 1992 to 1999. The participants provided information on their lifestyle using a self-administered questionnaire. Relative Risks (RR) and 95% CI were estimated using Cox proportional hazard models and adjusted for age, BMI and history of diabetes. During the follow-up, 52 participants died from pancreatic cancer. They found no significant association between alcohol consumption and pancreatic cancer death in men (HR 0.89, 95% CI 0.37-2.15) or women (HR 0.68, 95% CI 0.0.19-2.40), adjusting for age, smoking, body mass index and history of diabetes mellitus. There was a statistically significant increase in the risk of pancreatic cancer death in women who were current smokers at time of recruitment (HR 4.77, 95% CI 1.58-14.4) but not in men, although the confidence interval was very wide (HR 3.81, 95% CI 0.88-16.6).

16. Gapstur et al. (2011) examined the association of alcohol intake with pancreatic cancer mortality using data from the Cancer Prevention Study II, which was a large US prospective study of 1.2 million men aged 30 years or older. Details on alcohol consumption by participants were provided in a self-administered questionnaire. Hazard ratios (HR) and 95% CI were estimated using Cox proportional hazard models and adjusted for smoking, age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones or diabetes mellitus. The reference group in the analysis was non-drinkers. During the 24-year follow-up, 6847 participants died of pancreatic cancer. In general, the study observed a positive association between the amount of alcohol

consumed and pancreatic cancer mortality in age-adjusted analyses and in multivariable-adjusted analyses. For men, consumption of three drinks per day and of four or more drinks per day was associated with a statistically significantly increased risk of pancreatic cancer mortality (RR = 1.41, 95% CI 1.22 – 1.63 for 3 drinks a day and RR = 1.24, 95% CI 1.11 – 1.40 for ≥ 4 drinks per day). Similar results were obtained in the analyses of men and women combined consuming three drinks per day and four or more drinks per day (RR = 1.39, 95% CI 1.23 – 1.56 for 3 drinks a day and RR = 1.31, 95% CI 1.19 – 1.44 for ≥ 4 drinks per day). However, in their analysis of women alone, only those consuming four or more drinks per day had significantly elevated RR estimates (RR = 1.45, 95% CI 1.21 – 1.73). When the analysis was stratified by smoking status, alcohol intake was associated with pancreatic cancer mortality risk in both never smokers and in ever smokers. For example in their combined analysis of men and women, consumption of three or more drinks per day was associated with pancreatic cancer mortality in never smokers (RR = 1.36; 95% CI, 1.13-1.62) and in ever smokers (RR = 1.16; 95% CI, 1.06-1.27). They did not observe a statistically significant interaction between alcohol consumption and smoking status (P= 0.58 for interaction). The study also examined the effect of alcoholic beverage type on pancreatic cancer mortality. The found no association between beer and wine consumption and pancreatic cancer mortality in the total cohort (consumption of ≥ 3 beers/day RR = 1.08, 95% CI, 0.90-1.30 and for consumption of ≥ 3 wines/day RR = 1.09, 95% CI 0.79-1.49). However, consumption of three or more liquor drinks per day was associated with a significantly elevated risk of pancreatic cancer mortality in the total cohort (RR = 1.32, 95% CI 1.10 – 1.57).

17. Anderson et al. (2012) examined the association between alcohol and tobacco use and the age of presentation of pancreatic cancer using a multicentre international database for pancreatic cancer (Pancreatic Cancer Collaborative Registry (PCCR)). Participants provided details on their alcohol consumption and smoking using an online survey tool. 811 subjects formed the cohort for the study. HR and 95% CI were estimated using Cox proportional hazard models. They found that heavy alcohol consumption (> 39 g/ day) was associated with the highest risk for diagnosis of pancreatic cancer at an earlier age (HR = 1.62, 95 % CI 1.04 – 2.54) relative to those who drank mild-to-moderate amounts of alcohol. Independent of the dose effects of alcohol, subjects who stopped drinking more than 10 years before their diagnosis of pancreatic cancer had almost an identical risk for early age onset as non-drinkers (HR = 0.95, 95% CI 0.54 – 1.68) and had a significantly lower risk than subjects who quit < 10 years before diagnosis (HR =1.27, 95% CI 0.66 – 2.43) or those who were actively drinking at time of diagnosis (HR = 1.65, 95% CI 0.96 – 2.81).

Case-Control Studies in the General Population

18. Two case-controls have been published since the last IARC review (2012) (Table 3). Gupta et al. (2010) examined the association between alcohol consumption and pancreatic cancer in a population based case-control (532 cases comprising of 291 men and 241 women and 1701 controls comprising of 883 men and 818 women) study in the US. The study examined the associated exposure characteristics of timing of consumption onset, duration and dose including binge drinking. For this analysis, “binge drinking” was defined as consumption of five or more drinks per day

(70 g of alcohol). Participants self-reported their alcohol consumption history including information on the types of alcoholic beverage consumed over their lifetime. The ORs and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression and adjusted for a) age (in 5-year group) and b) age, energy intake, body mass index, race education, smoking, binge drinking, history of diabetes, and physical activity. The reference group for the analyses was those who never drank or drank less than one drink a month. In their analyses, the odds ratio (OR) increased with increasing duration and increasing dose of heavy alcohol consumption in men (Table 3). Men with the highest lifetime alcohol consumption has a greater than two-fold increased risk of pancreatic cancer (lifetime >35 drink/week, OR = 2.2, 95% CI 1.1 – 4.6, adjusted for all variables) compared to the referent group. Very few women consumed this amount of alcohol and so a similar anlaysis on women was not possible. Gupta et al. (2010) reported that a history of binge drinking conferred a 3.5 fold increased risk in men. This increased risk occurred regardless of age when binge drinking first occurred or when binge drinking last occurred. Pancreatic cancer risk was also positively associated with increasing average number of drinks consumed during the binging episode (e.g., 10 - 14 drinks, OR = 3.6, 95% CI 1.3 - 9.7 and > 14 drinks, OR = 4.4, 95% CI 1.4 - 13.0), with increasing years duration of binge drinking (6-10 years, OR = 2.9, 95% CI 1.1 – 7.8 and > 10 years, OR = 3.7, 95% CI 1.9 – 11.0) and with frequency of binge drinking each month. When the results were stratified by smoking status, in general, the risk of pancreatic cancer was greatest in the highest alcohol consumption group-related categories regardless of smoking status. However, results from the multivariate analyses suggested that heavy drinkers and the heaviest binge drinkers who were current smokers may be at the greater risk of pancreatic cancer than never or former smokers (binge drinking >10 years OR = 9.5, 95% CI = 1.8–50; ≥15 drinks/day during binge drinking OR = 9.5, 95% CI = 1.4–64; >35 drinks/week during the past 20 years OR = 4.2, 95% CI = 1.6–12). When the results were stratified by alcoholic beverage type, significant associations among men were observed for wine (OR = 2.8, 95% CI 1.2 – 6.3), consumption of both beer and liquor (OR =2.3, 95% CI 1.3 – 4.1), and the combination of wine, beer and liquor (OR = 1.7, 95% CI 1.0 – 2.8). These associations between alcoholic beverage type and pancreatic cancer risk were not observed among women. Overall, Gupta et al. (2010) found that alcohol consumption was associated with pancreatic cancer among men but not women, with increased risk ranging from 1.5 to 6.0-fold based on dose, duration and pattern of alcohol consumption reported.

19. Talamini et al. (2010) conducted a hospital based case-control study (326 cases and 652 controls) on pancreatic cancer in Italy. The study examined the association between alcohol consumption and pancreatic cancer risk and the possible interaction between tobacco and alcohol. Information on participant lifestyle habits were obtained by interview. ORs and 95% CI were calculated by means of multiple logistic regression and adjusted for year of interview, education, history of diabetes mellitus, smoking habits and body mass index. Interaction between tobacco and alcohol was assessed by synergistic index. The study found that both current and former drinkers were at increased risk of pancreatic cancer, although the results were not statistically significant (former drinkers, OR = 1.51, 95% CI 0.79 – 2.91 and current drinkers OR = 1.41, 95% CI 0.92 – 2.22). When the data were analysed by amount of alcohol consumed, a positive trend was observed with increasing alcohol intake, with

significant ORs for higher consumption (21-34 drinks/week OR = 2.03, 95% CI (1.10 – 3.74); ≥ 35 drinks/week OR = 3.42, 95% CI (1.79 – 6.55).

20. Klein et al. (2013) developed both a relative risk model that included established risk factors for pancreatic cancer and an absolute risk model for pancreatic cancer in the general population using data from the PanScan Consortium of 12 case-control studies nested within prospective cohorts and 8 retrospective case-control studies (3,349 cases and 3,654 controls). They used a logistic regression model for case-control status as a function of smoking history, history of diabetes, family history of pancreatic cancer, alcohol consumption, obesity and GWAS-identified risk markers adjusted for sex, age and study to build the relative risk model for pancreatic cancer. In the study population, they found heavy alcohol use (> 3 drinks/day) was associated with an increased risk of pancreatic cancer (OR 1.45, 95% CI 1.19 -1.76).

Overall Summary

21. Although the exact role of alcohol consumption in pancreatic cancer remains unclear, as other risk factors are also involved, it was possible to draw some conclusions from the new studies. Taking the data from the pooled analyses considered here and those considered previously (Michaud et. (2010); Lucenteforte et al. (2012); Genkinger et al., 2009 and Tramacere et al. (2010) along with the data from Gupta et al. (2010) on binge drinking (paragraph 18), low to moderate alcohol consumption (~ 3 drinks/day) is not associated with increased pancreatic cancer risk. However, heavier drinking (> 4drinks/day) may increase pancreatic cancer risk. The association between total alcohol intake and pancreatic cancer risk was not modified by smoking status, the major lifestyle risk factor for pancreatic cancer.

Questions for the Committee

1) What are the views of the Committee on the recently available epidemiological studies (case-control, cohort, pooled and meta-analysis) on alcohol exposure and pancreatic cancer risk?

2) Do the new studies add further weight to the statement by IARC (2012) that an association between alcohol consumption and cancer of the pancreas exists? Or do the new studies alter this view?

3) Do members think there is sufficient data to come to a conclusion about the amount of alcohol and nature of drinking i.e. cumulative per week, daily intake, type of alcohol and pancreatic cancer?

4) Thus far, does the data provided enable the Committee to make any definitive conclusions on the role of alcohol and pancreatic cancer?

5) This paper presents a narrative summary of each paper identified in the literature search and has used an informal qualitative assessment of the papers considered. In order to help identify key studies in the forthcoming papers for the discussions of this topic, do Members think a formal quality

scoring scheme or a formal qualitative assessment approach should be developed or adopted, accepting the additional time for preparation of review papers especially for a scoring scheme, or is the informal approach used up to now sufficient? If either formal approach is adopted, what criteria should be included?

PHE Toxicology Unit
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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Consumption of Alcohol and Pancreatic Cancer Risk

Extract from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 96: Alchol Consumption and Ethyl Carbamate
Pages: 602-617

Full document is available here:
http://monographs.iarc.fr/ENG/Monographs/vol96/mono96.pdf

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Extract from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100E: Personal Habits and Indoor Combustions
Pages: 388-390, 446-447, 472 and Tables 2.25, 2.26, 2.27 and 2.28

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