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

SACN Review of vitamin D. Adverse effects of high levels. Vitamin D and pancreatic cancer

Introduction

1. Members will recall that the Scientific Advisory Committee on Nutrition (SACN) is in the process of reviewing its recommendations on vitamin D. The COT has been asked to provide advice on high levels of vitamin D intake.

2. A paper providing an overview of vitamin D toxicity (TOX/2012/23) was considered in June 2012; it had been agreed that the 2011 review by the US Institute of Medicine Food and Nutrition Board (IOM, 2011) could be used as a bibliographic source.

3. One of the issues identified by IOM and considered in paper TOX/2012/23 was that of pancreatic cancer. When the US IOM reviewed vitamin D they noted that the studies investigating the association between serum 25-hydroxyvitamin D [25(OH)D] levels and pancreatic cancer had provided conflicting results with some, but not all, studies suggesting that there could be an increase in pancreatic cancer at higher levels of 25(OH)D. The IOM considered that the data showed a U shaped dose-response relationship and this was comparable with the dose-response relationship also seen for all-cause mortality (see paper TOX/2013/33). In interpreting these studies it should be noted that normal circulating levels of 25(OH)D are in the range 25-200 nmol/L.

4. The data on pancreatic cancer considered by the IOM can be summarised briefly as follows: Skinner *et al*., 2006 reported data from two large prospective studies, the Health Professionals Follow up Study (HPFS) and the Nurses' Health Study (NHS), which suggested that the relative risk (RR) of pancreatic cancer was lower in the highest four quintiles of vitamin D intake compared to the lowest quintile. Similarly, Giovannucci *et al*., 2006 observed that the risk of pancreatic cancer was lower in males from the HPFS with higher predicted serum 25(OH)D concentrations. In contrast, Stolzenberg-Solomon *et al*., 2006 reported that in individuals from the ATBC cohort of Finnish smokers with higher 25(OH)D levels, the risk of pancreatic cancer was higher. Subsequent analysis of data from the US Prostate, Lung, Colorectal and Ovarian Screening Trial (PCLO) cohort by the same group, suggested an increase in risk only in subjects with low annual solar exposure (Stolzenberg-Solomon *et al*., 2009) but a higher risk overall in individuals in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP) cohort (Stolzenberg-Solomon *et al*., 2010). However it has been argued that the observed U

shaped curve was a statistical artefact related to the chosen cut off points (Baggerly and Garland, 2012). The relevant section of TOX/2012/23 is attached at Annex A.

5. The COT considered the data on pancreatic cancer and all-cause mortality and concluded that the curve was reverse J shaped rather than U shaped, the minutes are as follows: *"Members considered that the J-shaped curve described for pancreatic cancer was of interest, but that the suggested relationships for other cancer endpoints were not convincing and that it would not be necessary to refer the question of carcinogenicity to the COC at this time".*

Additional data on vitamin D and pancreatic cancer risk

6. A number of additional studies on vitamin D and pancreatic cancer have been considered below. These were either not considered by the IOM in their 2011 review, or were published subsequently:

Individual studies

7. Bao *et al*., 2010 prospectively followed 118,597 participants in the NHS and the HPFS cohorts from 1986-2006. This study appears to be an expansion of the work done on the HPFS cohort by Giovanucci *et al*., 2006 (see Annex A for further details). A plasma 25(OH)D level was calculated[1] from known vitamin D predictors for each individual, and the predicted 25(OH)D level examined in relation to pancreatic cancer risk. RRs and 95%CI were estimated using Cox proportional hazards models adjusted for age, sex, race, height, smoking and diabetes. During 20 years (y) of follow up, 575 incident pancreatic cancer cases were identified. Higher predicted 25(OH)D score was associated with a significant reduction in pancreatic cancer risk as shown in Table 1. The results were similar when adjusted for BMI and physical activity.

Table 1. Relative risk of pancreatic cancer for predicted 25(OH)D concentration (Bao *et al*., 2010)

Quintile nmol/L	Cases	Person years	RR (95%CI)
18.22-62.9	125	444,248	1.00 (referent)
62.9-68.39	121	445,430	0.65 (0.50-0.85)
68.39-72.63	115	443,622	0.85 (0.65-1.09)
72.63-77.63	112	443,944	0.77 (0.59-1.00)
77.88-96.35	102	449,015	0.72 (0.55-0.94)

[1] The predicted 25(OH)D score was derived as follows; for a sample of 1095 men in the HPFS who had plasma 25(OH)D concentrations available as the dependent variable, linear regression was performed using race, geographic region, vitamin D intake, BMI, and leisure time physical activity as independent predictors of plasma 25(OH)D. Then on the basis of the predictors regression coefficients from the sample, a 25(OH)D score was calculated for each cohort member. To validate this model, the 25(OH)D score was calculated from an independent sample of 542 men in the HPFS study who also had available measurements of circulating 25(OH)D. The actual plasma concentration rose across increasing deciles of 25(OH)D score (P_{trend} <0.001) the difference in the mean actual 25(OH)D concentration between extreme deciles was 10 ng/ml^{-1} (24.96 nmol/L) similar to the difference of 11 ng/ml^{-1} (27.46 nmol/L).

8. Bao *et al*. (2010) noted the inconsistent results reported in other studies, with a lower risk of pancreatic cancer being associated with higher vitamin D status in the NHS and HPFS studies and a higher risk in the ATBC study, could be due to the participants of the studies not being comparable. The individuals in the ATBC cohort were male, current smokers and were living in Northern latitudes (Finland). Since their own study found a stronger inverse association between pancreatic cancer and vitamin D status in non-smokers and those living in the Southern states it was possible that the effect differed between population groups. It was also suggested that since dietary vitamin D was largely supplied by dairy products in the US and by fish in Finland, the fish-rich diet of the Finnish population could also contain pancreatic carcinogens such as organochlorines. It was further noted that whereas actual blood 25(OH)D levels most likely reflected recent exposure, the predicted 25(OH)D score took into account long term factors such as race or residential region which could be a more stable marker. The correlation between plasma levels 4 y apart was 0.7 for actual measures and 0.83 for the 25(OH)D predicted scores. However, it should be noted that there was little difference in predicted and actual levels when the model was validated.

9. In a case-control study in adults from the San Francisco bay area of the US, dietary intake of vitamin D and of calcium was associated with an increased risk of pancreatic cancer (Zablotska *et al*., 2011). To explore the association between intake of vitamin D from diet and supplements, dietary data from a semi-quantitative food frequency questionnaire were analysed. There were 532 eligible pancreatic cancer cases (aged 21-85 y); these were compared with 1701 eligible controls. Relative to controls, in the cases there were a higher proportion of Black/African Americans, with fewer y of education and they were more likely to smoke and to be in the highest quartile of total energy intake, to be overweight and to have been diagnosed with diabetes. In general, the risk of pancreatic cancer increased with intake of vitamin D from food only in men, but not in women as in Table 2.

Table 2. Risk of pancreatic cancer and vitamin D intake from food only (Zablotska *et al*., 2011).

Vitamin D intake µg/day (food only)						
	Men			Women		
	Case	Control	OR(95%CI)	Case	Control	OR(95%CI)
<3.75	29	119	1 referent	21	72	1 referent
3.75-7.48	91	255	1.6 (0.95-2.6)	59	198	1.3 (0.70-2.6)
7.5-11.23	37	93	2.0 (1.1-3.8)	38	97	2.1 (1.01-4.2)
≥ 11.25	13	29	2.6 (1.1-6.0)	9	38	0.93 (0.35-2.5)
			Trend-*p* 0.009			Trend-*p* 0.41

10. For total intake vitamin D (food and supplements) risk increased with intake until the last intake category of intake (≥ 20 µg/day) where the risk was less than 1 and not different from those with intakes less than (10 µg/day) (see Table 3).

Table 3. Risk of pancreatic cancer and vitamin D intake from food and supplements (Zablotska *et al*., 2011).

Vitamin D intake µg/day (food + supplements)	Men			Women		
	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)
<5	49	224	1 referent	44	163	1 referent
5-9.98	103	255	2.0 (1.4-3.1)	70	213	1.5 (0.96-2.4)
10-14.98	71	164	2.2 (1.4-3.4)	39	141	1.1 (0.66-1.9)
15-19.98	49	141	2.2 (1.4-3.6)	45	175	1.2 (0.71-1.9)
≥ 20	16	99	0.91 (0.47-1.7)	39	126	1.4 (0.84-2.4)
			Trend-*p* 0.45			Trend-*p* 0.64

11. Men with the highest dietary vitamin D intake without supplements (≥ 11 µg/day) had a 2.6 fold increased risk of pancreatic cancer compared with men in the lowest intake (< 3.75 µg/day, trend p= 0.009). No statistically significant associations were observed among women. When participants who took supplements were included in these analyses, dietary vitamin D intake remained statistically associated with increased risk of pancreatic cancer (for highest vs lowest), the OR in men was 1.4 (trend-*p*=0.02) and in women 1.1 (trend-*p*=0.09); the data for the latter analyses were not given in the paper. Dairy foods were the major source of dietary vitamin D, but when the models were adjusted for intake of dairy foods, the increased association remained unchanged (OR (95%CI = 1.6 (0.91-2.7), 1.9(0.94-3.8) and 2.3 (0.88-5.8) for increasing categories of vitamin D intake.

12. To further explore the unexpected increased risk of pancreatic cancer associated with high levels of circulating vitamin D reported by Stoltzenberg-Solomon and colleagues, Weinstein *et al*., (2012) examined the role of vitamin D binding protein (DBP)[2]. Pre-diagnostic DBP and 25(OH)D levels were studied in a nested case control study of 234 cases and 234 controls from the ATBC study of Finnish male smokers. The OR(95%CIs) were estimated using logistic regression. Increasing serum 25(OH)D concentration was positively associated with risk of pancreatic cancer (Table 4). None of the patterns appeared monotonic and statistical significance was achieved for the highest quartile only.

[2] Vitamin D binding protein transports vitamin D compounds in circulation, binding approximately 88% of the 25(OH)D and 85% of the active hormonal form 1,25-dihydroxyvitamin D (1,25(OH)D2. In addition, 12 and 15% respectively are bound to albumin leaving very little free vitamin D. Current Analytical methods do not distinguish free and bound vitamin D.

Table 4. OR (95% CI)s for the association between DBP, 25(OH)D and 25(OH)D: DBP molar ratio and risk of pancreatic cancer, ATBC study, 1985-2004.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
25(OH)D[a]					
Case/control	48/60	61/58	50/59	74/56	
Model 1*	1.00	1.33 (0.79-2.24)	1.14 (0.65-1.98)	1.78 (1.02-3.11)	0.08
Model 2[§]	1.00	1.51 (0.87-2.62)	1.21 (0.68-2.17)	1.91 (1.05-3.46)	0.07
Model 3[ǂ]	1.00	1.42 (0.89-2.49)	1.28 (0.71-2.33)	1.81 (0.97-3.37)	0.10
25(OH)D:DBP molar ratio[b]					
Case/control	55/59	52/58	38/58	88/58	
Model 1*	1.00	1.09 (0.59-2.03)	0.81 (0.43-1.53)	1.89 (1.01-3.54)	0.04
Model 2[§]	1.00	1.00 (0.52-1.92)	0.77 (0.39-1.50)	1.86 (0.97-3.56)	0.04

[a] Vitamin D was measured by RIA or chemiluminescence. Season specific/laboratory-specific quartiles for the RIA data were Q1: ≤31.5, Q2 >31.5 and ≤45.1, Q3: >45.1 and ≤ 56.7. Q4 >56.7 nmol/L for the darker months and Q1: ≤40.9, Q2 >40.9 and ≤54.7, Q3: > 54.7 and ≤ 73.4. Q4 >73.4 nmol/L for the summer months and for the CLIA data Q1: ≤18.4, Q2 >18.4 and ≤26.8, Q3: >26.8 and ≤ 40.3, Q4 >40.3 nmol/L for the darker months and Q1: ≤29.0, Q2 >29.0 and ≤41.5, Q3: >41.5 and ≤61.8. Q4 >61.8 nmol/L for the summer months

[b] The range for the molar ratio of 25(OH)D: DBP was Q1 ≤4.91, Q2 >4.91 and ≤8.07, Q3 >8.07 and ≤11.03, Q4 >11.03.

* Model 1 is conditioned on the matching factors of age and date of blood collection.

[§] Model 1 is conditioned on the matching factors of age and date of blood collection and adjusted for BMI, smoking, diabetes, occupation physical activity, education, ethanol intake, and serum retinol, cholesterol, β-carotene and α-tocopherol.

[ǂ] As model 2, with additional adjustment for either 25(OH)D or DBP respectively.

13. DBP and 25(OH)D levels were correlated and DBP was inversely associated with pancreatic cancer risk (OR (95%CI) = 0.6 (0.39-1.12) for the highest vs lowest quartile (P_{trend} = 0.02); the DBP quartiles were ≤ 4,026, > 4,026 & ≤5,329, > 5,329 & ≤ 6,721 and 6,721 nmol/L; the mean serum 25(OH)D concentration for these quartiles was 31.5, 39.2, 45.1 and 49.9 nmol/L respectively. The association appeared to have a threshold between quartiles 2 to 4 and quartile 1 (so that the risk in quartiles 2-4 was lower than in quartile 1) and was primarily evident among the men with concurrent high 25(OH)D concentrations (OR (95%CI) = 0.33 (0.16- 0.70) for highest vs lowest quartile (P_{trend} = 0.002)) with no association for men with lower serum 25(OH)D (1.28 (0.62- 2.61) for highest vs lowest quartile (P_{trend} = 0.63, $P_{interaction}$ = 0.01). Men with higher 25(OH)D concentrations and serum DBP below the median showed greatly elevated risk of pancreatic cancer (5.01 (2.33-10.78) for highest vs lowest quartile (P_{trend} = 0.0001)) while risk was weakly inversely associated with serum 25(OH)D when DBP concentrations were higher ($P_{interaction}$ = 0.01). When the data were analysed as quintiles (as had been the case for the previous Stolzenberg-Solomon study), the OR for the highest vs lowest quintiles was 2.01(1.08-3.72, P_{trend} = 0.03). Risk estimates were slightly stronger with multivariate adjustment for circulating DBP. When calculated as a 25(OH)D:DBP molar ratio (a surrogate for free vitamin D) the risk of pancreatic cancer was elevated in a similar manner to that for 25(OH)D alone) although again, the patterns did not seem monotonic. Using an estimate of free 25(OH)D resulted in the same risk estimates as

those for the molar ratios. The authors concluded that, taken together, the findings indicated that higher DBP concentration may sequester more 25(OH)D and reduce free 25(OH)D bioavailability. The authors noted the “free hormone” hypothesis which suggests that only free hormones are able to enter target cells and influence transcriptional and downstream events. The authors also noted that it was unclear whether the findings were generalizable to non-smokers or women. It was pointed out that the risk of pancreatic cancer was elevated at higher 25(OH)D concentrations in the VDPP cohort (Stolzenberg Solomon *et al*., 2010) than in the ATBC study, where vitamin D status was generally lower due to latitude and time of sampling (which was not generally done in the summer month) as well as the low use of supplements in the ATBC population.

14. Polymorphisms in the VDR gene have been shown to affect VDR messenger RNA and protein levels which in turn may affect the immunomodulatory function of VDR. Approximately 200 different VDR single nucleotide polymorphisms (SNPs) have been described; however, the VDR polymorphisms which are most frequently associated with tumorigenesis are *Fok*I, *Bsm*I, *Taq*I, *ApaI, Eco*RV and Cdx2 with the most frequently studied DNPs being the restriction fragment length polymorphisms (RFLPs) *Fok*I and *Bsm*I. Li et al. (2013) conducted a pilot study, to investigate the effect of vitamin D receptor gene polymorphisms on the risk of pancreatic cancer. Two single-nucleotide polymorphisms were investigated in 91 prostate cancer patients and 80 age and sex matched controls. The samples were genotyped for *Fok*I (rs2228570) and *Bsm*I (rs1544410) polymorphisms using the PCR and restriction fragment length method. Chi-square analysis was used to test for the overall association of the VDR genotype with disease. The *Fok*I RFLP is located in the coding region of the VDR gene and leads to the production of a VDR protein which is 3 amino acids longer than normal. Although no significant differences in ligand activity, DNA binding or transactivation activity have been identified between these two VDR forms, the shorter VDR variants exhibits higher potency than the longer one. The *Bsm*I RFLP is intronic and located at the 3' end of the gene. *Bsm*I does not alter the amounts, structure or function of the final VDR protein produced, but it is strongly linked with a poly (A) repeat and may affect VDR mRNA stability. Thus, VDR polymorphisms may have important implications for VD signalling and are associated with various malignancies. There was a significant difference in the frequency of the FF genotype between the pancreatic cancer patients and controls (P_{trend} = 0.009). However the difference in frequency of genotype BB between the two groups was not significant (P_{trend} = 0.082). The difference between the FF and ff frequency was significant (P=0.002). The two high risk genotypes were ffbb and Ffbb with an 11.66 and 6.42 fold increased risk of pancreatic cancer respectively. The authors concluded that heterozygous variants of *Fok*I were associated with a decreased risk of pancreatic cancer in a North Chinese population, whereas the effects of *Bsm*I were not significant. VDR genotypes were important for the development of pancreatic cancer in the study population but the implications of the findings needed to be explored further.

15. Anderson *et al*. (2013) analysed the association between 87 SNPs in 11 genes and pancreatic cancer risk in the Ontario Pancreas Cancer study, a population-based case control study. In this study, 628 pancreatic cancer cases were matched with 1193 controls identified through random digit dialling. Age and sex adjusted odds ratios and 95%CIs were estimated by multivariate logistic

regression. SNPs in the *CYP24A1*, *CYP2R1*, calcium sensing receptor (*CASR*), vitamin D binding protein (*GC*), retinoid X receptor-alpha (*RXRA*) and megalin (low density related lipoprotein 2) (*LRP2*) genes were significantly associated with pancreatic cancer risk. For example, pancreatic cancer risk was inversely associated with *CYP2R1* rs 10741657 (AA versus GG), OR = 0.70; 95%CI 0.51-0.95) and positively with CYP24A1 rs6127119 (TT versus CC, OR = 1.94; 95%CI 1.28-2.94). However, none of the associations were statistically significant after adjustment for multiple comparisons.

Meta-analysis

16. Wolpin *et al*. (2011) conducted a pooled analysis of nested case control studies with a total of 451 cases and 1,167 controls from 5 cohorts. The cohorts were from the HPFS, the NHS, the Physicians Health Study (PHS), the Women's Health Initiative-Observational Study (WHI) and the Women's Health Study (WHS), with follow up periods ranging from 12.2 to 25.3 y. Logistic regression was used to compare the odds of pancreatic cancer by plasma 25(OH)D level. Mean plasma 25(OH)D was lower in cases than controls (61.3 vs 64.5 nmol/L). In logistic regression models plasma 25(OH)D was inversely associated with odds of pancreatic cancer. Several multivariate models were used but the results were presented adjusted for age, cohort, sex, BMI, smoking status, history of diabetes, multivitamin use and month of blood draw (Table 5). Nearly 90% of the participants were white and 54-81% of them, female. It was noted that the participants were from a wide range of geographic locations, which was considered to be a strength of the study (however, if Bao *et al*., 2010 are correct, the diverse geographical locations could obscure any associations).

17. Compared with those individuals with insufficient levels of 25(OH)D (<50 nmol/L) the ORs were 0.75 (0.58-0.98) for subjects with relative insufficiency (50 to <75 nmol/L) and 0.71 (0.52-0.97) for those with sufficient levels (≥75 nmol/L) respectively. No increase in risk was apparent in individuals with 25(OH)D levels ≥100 nmol/L compared to those with relative insufficiency. For the latter analysis, there were noted to be 27 cases and 79 controls with plasma 25(OH)D levels ≥100 nmol/L compared to 189 cases and 524 controls in the relatively insufficient referent category.

Table 5. Risk of pancreatic cancer associated with plasma 25(OH)D levels (*Wolpin et al*., 2011)

Quintile 25(OH)D (nmol/L)	multivariable-adjusted ORs (95%CI)
<45.6	1.0 referent
45.6-56.9	0.76 (0.56-1.10)
56.9-66.9	0.75 (0.53-1.06)
66.9-81.1	0.68 (0.48-0.97
>81.1 nmol/L	0.67 (0.46-0.97),
	$P_{\text{trend}} = 0.03$

U shaped curve- comments

18. In a commentary on Stolzenberg-Solomon *et al*., 2006, Michaud (2006) noted a number of difficulties arising in conducting epidemiology studies but concluded that Stolzenberg-Solomon *et al*., 2006 was well designed and conducted. The results were not consistent with those from other studies, notably the results from the HPFS study, and it was suggested that this might be due to smoking; the HPFS cohort was a population of health professionals with a low prevalence of smoking, whereas ATBC recruited only current smokers (this population was also found to have an increased risk of lung cancer in the β-carotene intervention arm). It was possible that the results might be due to confounding from smoking, which was a strong risk factor for pancreatic cancer and associated with numerous behavioural and lifestyle factors; it was unlikely that the smoking itself is was the problem, but an unknown risk factor associated with it. Other possibilities suggested were UV exposure having an immunosuppressive effect, and an unknown pancreatic carcinogen present in fish. However, it was possible that the result was a real one and if so it might be more likely to apply specifically to smokers, particularly those with low vitamin D status.

19. Grant (2009) reviewed all the areas for which a U shaped curve was suggested and agreed that the most likely explanation with regard to pancreatic cancer was that the relationship between vitamin D and pancreatic cancer is different for smokers and non-smokers. Similar conclusions were drawn by Bulathsinghala *et al*., 2010 who noted that the U shaped curve had not been observed in all studies which could be due to the differences in pancreatic cancer risk between men and women and between smokers and non-smokers. Grant (2009) further noted that Stoltzenberg-Solomon *et al*., 2009 did not find an association overall, but found that there were positive associations between 25(OH)D with low estimated annual residential UVB exposure but not with high or moderate exposure.

20. The World Cancer Research Fund (WCRF) and American Institute of Cancer Research Second Expert report (WCRF, 2006) did not draw any conclusions on the relationship between vitamin D and pancreatic cancer. Similarly, no conclusions were drawn by the Systematic Literature Review Continuous Update project (WCRF, 2011).

21. Klapdor *et al*., (2012) reported that patients with pancreatic disease including pancreatic cancer had low vitamin D status compared to controls.

Summary and discussion.

22. A number of studies have been conducted to investigate the association between vitamin D intake or status (blood 25(OH)D) and the risk of pancreatic cancer. The results of these are conflicting, with high vitamin D intake or status being associated with both an increase and decrease in the risk of pancreatic cancer. The most notable results linking high vitamin D and pancreatic cancer have come from the Finnish ATBC cohort of smokers, but studies in other populations have reported similar findings.

23. The reasons for the differing results are uncertain, it has been suggested that an unidentified confounding factor related to smoking or to fish consumption could be responsible and low solar radiation exposure has also been proposed as an explanation, suggesting that any association between high vitamin D levels and increased risk of pancreatic cancer may not be generalizable to the whole population. Recent data on vitamin D binding protein suggests that free vitamin D, rather than circulating levels may be important. However, other commentators have proposed that the finding may be a statistical artefact and that a U-shaped curve does not exist.

Questions for the Committee

24. The Committee is asked:

i. Whether the U (or reverse J) shaped curve is significant?

ii. Can any conclusions be drawn about high levels of vitamin D and pancreatic cancer for the general population?

iii. Can any conclusions be drawn about high levels of vitamin D and pancreatic cancer for specific population groups?

iv. Whether this issue should be referred to COC?

Secretariat

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Glossary

AICR: American Institute of Cancer Research
ATBC: Alpha Tocopherol-Beta Carotene
BMI: Body Mass Index
CI: Confidence Intervals
COC: Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.
CYP: cytochrome P450
DBP: vitamin D binding protein
HPFS: Health Professionals Follow up Study
25(OH)D: 25-hydroxyvitamin D
IOM: Institute of Medicine Food and Nutrition Board
NHS: Nurses' Health Study
OR: Odds Ratio
PCLO: Prostate, Lung, Colorectal and Ovarian Screening Trial
PCR: Polymerase chain Reaction
Poly(A): Polyadenylation
RFLP: Restriction Fragment Length Polymorphism
SACN: Scientific Advisory Committee on Nutrition
SNP: Single Nucleotide Polymorphism.
US: United States of America
VDPP: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers
VDR: Vitamin D Receptor
WCRF: World Cancer Research Fund

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCT AND THE ENVIRONMENT

SACN Review of vitamin D. Adverse effects of high levels. Vitamin D and pancreatic cancer

78. Some observational studies suggest that higher serum 25 OHD levels are associated with an increased risk of pancreatic cancer. Skinner *et al*., (2006) reported data from 2 large prospective studies; 46,771 men aged 40-75 in the Health Professionals Follow-up study and 75,427 women aged 38-65 in the Nurses' Health study. 365 incident cases of pancreatic cancer were identified over 16 y of follow-up. Compared with participants in the lowest category of vitamin D intake (<3.75 µg (150 IU)/day) pooled multivariate risks were:

Table 10. Relative Risks of pancreatic cancer referent to the highest quintile of serum 25(OH)D from Skinner *et al*., 2006

Vitamin D µg (IU)/day	RR (95%CI)
<3.75[3] (150)	1.0
3.75-7.48 (150-299)	0.78 (0.59-1.01)
7.5- 11.23 (300-449)	0.57 (0.40-0.83)
12.25- 14.98 (450-599)	0.56 (0.36-0.87)
≥ 15 (600)	0.59 (0.40-0.88)
P trend = 0.01	

The associations may have been stronger in men than women. After adjusting for vitamin D intake, calcium and retinol intakes were not associated with pancreatic cancer risk. Dietary information was obtained by semi-quantitative food frequency questionnaires conducted in 1984 and 1986 in the NHS and HPFS study

[3] This has been corrected, the original version in paper TOX/2012/23 gave this figure as 37.5 µg Skinner *et al*., 2006 reported data from two large prospective studies (HPFS and NHS) which suggested that the relative risk of pancreatic cancer was lower in the higher four quintiles of vitamin D intake, similarly, Giovannucci *et al*., 2006 observed that risk was lower in males from the HPFS with higher predicted serum 25(OH)D concentrations. In contrast, Stolzenberg-Solomon *et al*., 2006 reported that the risk of pancreatic cancer was higher in individuals with higher 25(OH)D levels from the ATBC cohort of Finnish smokers. Subsequent analysis of the PCLO cohort suggested an increase in risk only in subjects with low annual solar exposure (Stolzenberg-Solomon *et al*., 2009) but a higher risk overall in individuals in the VDPP cohort (Stolzenberg-Solomon *et al*., 2010). However it has been argued that the observed U shaped curve was a statistical artefact related to the chosen cut off points.

respectively. The model was adjusted for age, time period, total energy intake, smoking, diabetes, BMI, height, region of residence, parity and multi-vitamin supplement use. It was noted that 95% of men and 94% of women in the highest categories of vitamin D intake were supplement users; when supplement users were excluded from the analysis, the inverse relationship between vitamin D intake and pancreatic cancer risk was still observed.

79. Similarly, Giovannucci *et al*, 2006 reported that a reduced risk of total cancer mortality and digestive (including pancreatic) cancer was associated with increased serum levels of 25(OH)D. The intention of the study was to explore whether the increased cancer mortality seen in Black men and women might reflect differences in vitamin D status. The analysis was conducted in 43,949 men from the HPFS study. The level of 25(OH)D was predicted from vitamin D intake assessed by food frequency questionnaire and a pilot study measuring 25(OH)D levels in 1095 men from the study.

80. In contrast, Stolzenberg-Solomon *et al*., (2006) found that in a nested case control in subjects from the Alpha-Tocopherol, Beta Carotene Cancer Prevention (ATBC) study cohort of Finnish male smokers aged 50-69y at baseline, there was a positive association between higher serum 25(OH)D and risk of pancreatic cancer. In this study, 200 incident cases were identified from the cohort and matched with 400 controls by age and month of baseline blood draw. Information on diet was obtained by a validated self-administered questionnaire prior to randomisation. Odds ratios were calculated using conditional logistic regression. Variables examined in analyses and as potential confounders were age, smoking history, education, residence in city, height, weight, BMI, blood pressure, a range of medical conditions including pancreatitis), dietary nutrients from food, and supplements, alcohol intake, serum nutrients, occupational and leisure physical activity and season. Higher vitamin D concentrations were associated with a 3-fold increase in risk of pancreatic cancer (highest vs lowest quintile, >65.5 vs<32.0 nmol/L, OR 2.92; 95%CI 1.56-5.48, $P_{\text{trend}} = 0.001$, after excluding cases early during follow up).

81. However in a subsequent study nested case-control study conducted in the US Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO cohort) of 152, 810 men and women aged 55-74 y (Stolzenberg-Solomon, 2009). In the follow up period (11.7y) 184 incident cases of pancreatic cancers were identified and matched with 368 controls by age, race, sex and calendar data of blood draw. Blood samples were taken at baseline and dietary information (including supplement use) was obtained by food frequency questionnaire also at baseline. Odds ratios were calculated using conditional logistic regression, adjusting for smoking and BMI. Vitamin D concentrations were not associated with pancreatic cancer overall (highest vs lowest quintile, >82.3 vs <45.9 nmol/L (32.9 vs 18.4 ng/ml), OR 1.45; 95%CI 0.66-3.15, $P_{\text{trend}} = 0.49$). However, positive associations were observed among subjects with low estimated annual residential solar UBV exposure (based on geographical exposure) but not among those with high annual exposure ($P_{\text{interaction}} = 0.015$).

82. To resolve these conflicting findings, a pooled nested case-control study of several cohorts was conducted within the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (VDPP) (1974-2006) (Stolzenberg-Solomon *et al*., 2010). In total, 952 incident cases of pancreatic cancer were identified during a median

follow up period of 6.5y. Controls (n= 1,333) were matched to each case by cohort, age, sex, race/ethnicity, date of blood draw and follow up time. Conditional logistic regression analysis was use to calculate, smoking, BMI and diabetes adjusted odds ratios and 95% confidence intervals for pancreatic cancer. No significant associations were observed for participants with lower 25(OH)D status and pancreatic cancer. However, a high 25(OH)D concentration (≥ 100 nmol/L, 40 ng/ml) was associated with a statistically significant 2-fold increase in pancreatic risk overall (OR 2.12, 95%CI 1.23-3.64).

Table 11. Relative Risks of pancreatic cancer referent to the highest sextile of serum 25(OH)D from Stolzenberg-Solomon *et al*., 2010

25(OH)D nmol/L (ng/ml)	RR (95%CI)
<25 (10)	1.0
25-37.5 (10-15)	1.04 (0.74-1.44)
37.5-50 (15-20)	1.10 (0.79-1.55)
50-75 (20-30)	1.06 (0.76-1.48)
75-100 (30-40)	1.08 (0.73-1.59)
≥ 100 (40)	2.24 (1.22-4.12)
P trend 0.14	

The study cohorts were the ATBC study, CLUE, the Cancer Prevention Study II Nutrition Cohort, the New York University Women's Health Study (NYU-WHS), the Multiethnic Cohort Study (MEC), the PLCO study, and the Shanghai Women's and Men's Health Studies (SWHS and SMHS). Median serum 25(OH)D levels were comparable between cases and controls, but ranged from 33.4 to 64.7 nmol/L (13.36- 25.88) in the different cohorts. The increased risk in the highest category of serum 25(OH)D persisted even after the exclusion of cases diagnosed within the first 2 y after blood draw, leaving 558 cases and 840 controls (OR 2.20, 95%CI 1.22-3.96). The odds ratios were similar when the analyses were restricted to US cohorts only or when each cohort was excluded in turn. There was no significant interaction by use of vitamin D supplements or multivitamins. The authors noted that this analysis differed from the previous 2 analyses by the use of clinically relevant cut-points.

83. The findings of Stolzenberg-Solomon were disputed by Baggerly and Garland (2012) who argued that the U shaped curve was a statistical artefact associated with the chosen cut-off point groupings and that there was no U shaped curve to be explained. They demonstrated this by merging groups 5 and 6 (75-<100 and ≥ 100 nmol/L) together which produced ORs of 1.22, 1.09, 1.09, 1 and 1.07 for quintiles <25, 25-<37.5, 37.5 -<50, 50-<75 and ≥75 nmol compared to ORs of 1.22, 1.09, 1.09, 1, 0.95 and 1.77 for the groups <25, 25-<37.5, 37.5 -<50, 50-<75, 75-<100 and ≥100 nmol.