2. Studies of Cancer in Humans

2.1 Introduction

Ingestion of nitrate and nitrite can result in the endogenous formation of *N*-nitroso compounds in the presence of nitrosatable precursors that are contained in meats, fish and some common drugs (see Sections 1 and 4). Nitrate is ingested from dietary sources and drinking-water. Vegetables are usually the primary source when levels of nitrate in the drinking-water are below 50 mg/L, which is the regulatory limit in many countries. Many vegetables contain vitamin C and other compounds such as polyphenols that inhibit endogenous nitrosation. Whereas nitrate from both vegetables and drinking-water is reduced in the body to nitrite, sources from vegetables probably result in less endogenous formation of *N*-nitroso compounds because of the presence of inhibitors of nitrosation (see Section 1). For these reasons, the Working Group evaluated ingested nitrate from dietary sources and drinking-water separately.

Epidemiological studies that assessed the relationship between nitrate in the drinking-water and cancer have been primarily ecological in design and focused on stomach cancer. Fewer case–control and cohort studies were available for other cancer sites. Ecological studies can provide important information on causal inference when exposure circumstances contrast greatly (between regions or population subgroups) and migration of populations is limited, particularly if there is almost homogenous exposure within each region and there are no serious potential confounders (see Cantor, 1997; IARC, 2004).

However, inference from ecological studies of exposure to waterborne nitrate is more difficult because of the complexity of and intra-individual variation in endogenous nitrosation (see Section 4). Specific subgroups of a population that have higher exposure to nitrosation precursors (from nitrate in water and amines and amides in the diet) and lower exposure to inhibitors of nitrosation (e.g. dietary antioxidants) are probably at highest risk. Ecological studies of nitrate in drinking-water, therefore, are not liable to be highly informative unless levels of exposure are high and exposure to waterborne nitrate and other factors that affect nitrosation are homogeneous across the population groups. Therefore, the Working Group gave much greater weight to case–control and cohort studies in their evaluation.

Most case–control and cohort studies of exposure to nitrate in the drinking-water have been conducted in areas where levels of nitrate in drinking-water supplies are elevated due to the use of nitrogen fertilizers. Some of the highest levels of nitrate are found in shallow wells and surface water supplies which contain high levels in the spring due to run-off of excess nitrogen (see Section 1.4.2). Public water supplies are monitored routinely, and historical data on levels of nitrate are available; however, exposure to levels greater than the maximum contaminant limit in the USA of 10 mg/L (as nitrate-N) (Environmental Protection Agency, 2003) or the WHO drinking-water guideline of

50 mg/L as nitrate (WHO, 2004) are rare. Private wells tend to contain higher levels of nitrate than public supply wells because they are unregulated, are frequently shallower and more poorly constructed and are often located in close proximity to sources of contamination by nitrogen (crop fields, animal feed lots, septic tank systems). Since historical data from monitoring are available, most studies have focused on populations who use public water supplies and have excluded populations who use private wells with potentially higher exposures.

Occupational groups that may be at risk of ingesting nitrate were also considered. Workers in the manufacture of nitrate-based fertilizer can have high exposures to dusts that contain nitrate (> 10 mg/m^3) (see Section 1). One study (Al-Dabbagh *et al*., 1986) among men whose jobs entailed exposure to different levels of nitrates in dust (maximum, 5 mg/m^3) demonstrated that, at the end of a workday, salivary nitrate levels from highly exposed workers were approximately twice those of workers who had no exposure to nitrate in dust; however, dietary intake of nitrate was not controlled and the range of salivary levels of nitrate among highly exposed workers overlapped with those of unexposed men in several regions of England. Furthermore, a twofold variation in nitrate in saliva in non-occupationally exposed groups has been observed even under controlled conditions (Weisenberg *et al*., 1982; Bos *et al*., 1988). The Working Group considered that the evidence for exposure to nitrate via ingestion was lacking in these studies and could not be quantified; these studies were therefore not reviewed.

A few case–control studies have investigated exposure to nitrate from tap-water and have measured levels of nitrate and/or nitrite at the current residence or at the residence at the time of diagnosis of disease. Levels of nitrate and/or nitrite may change over time; therefore, considerable misclassification of exposure may occur if current levels of exposure are used to estimate past exposure. Variation in levels of nitrate across the distribution system of a public water supply could also introduce misclassification of exposure. In addition, nitrate and/or nitrite in water may be correlated with other environmental exposures such as agricultural pesticides that may be potentially relevant to some cancers.

Dietary intake of nitrite occurs primarily from the consumption of cured meats and fish, bakery goods and cereal products. Nitrite is also found as a contaminant of drinking-water but only in unusual circumstances (see Section 1.5). Several epidemiological studies evaluated the risk for specific cancers among subjects who had a higher intake of nitrite and a lower intake of vitamin C; this dietary pattern is liable to result in an increase in the endogenous formation of *N*-nitroso compounds. Studies of this design were considered by the Working Group to be particularly informative in the evaluation of human carcinogenicity.

Studies that estimated intake of nitrite from all dietary sources were reviewed, but these that only evaluated consumption of cured meat and risk for cancer were not reviewed specifically since they do not represent complete dietary nitrite intake. This is because many, but not all, cured meats contain nitrite and because other foods can also be

important sources of nitrite. The Working Group also noted the results of some studies that estimated intake of nitrite and preformed *N*-nitroso compounds.

Several ecological studies in high- and low-risk areas for stomach and oesophageal cancers evaluated the potential for endogenous formation of *N*-nitroso compounds using the *N*-nitrosoproline (NPRO) test developed by Ohshima and Bartsch (1981). Some studies also measured urinary excretion of nitrate, levels of nitrate and nitrite in the saliva and excretion of other specific *N*-nitroso amino acids. Excretion of NPRO was generally higher in high-risk areas; however, not all of the differences were statistically significant (Bartsch *et al*., 1992; van Maanen *et al*., 1996). Urinary and salivary levels of nitrate reflect exposures to nitrate from both dietary sources and drinking-water; therefore, these studies were evaluated as a separate group. However, the Working Group did not give substantial weight to these studies in their evaluation because of the ecological study design and because recent excretion of nitrate or levels of nitrate in saliva may not reflect past exposures.

2.2 Stomach and oesophageal cancer

2.2.1 *Ingested nitrate*

(a) Ecological studies (Table 2.1)

Several ecological studies have considered the relationship between exposure to nitrate and the risk for stomach or oesophageal cancer; most of these used mortality as the end-point. The concentration of nitrate in the drinking-water was often used as indicator of exposure, and some studies assessed its correlation with the occurrence of disease or investigated the differences in mortality or incidence of disease across exposure levels. Alternatively, the concentrations of nitrate were compared in populations who were classified according to different levels of risk. In many instances, urinary excretion of nitrate or its concentration in other body fluids in groups of individuals were used as indicators of exposure rather than levels in drinking-water and food. The main features and results of these studies are summarized in Table 2.1.

(i) *Nitrate in the drinking-water*

Asia

Two studies addressed the association between exposure to nitrate and the occurrence of tumours of the stomach and oesophagus in China. An early study (Wang *et al*., 1979) reported a positive significant correlation ($r = 0.23$) between concentrations of nitrate in the drinking-water (mean, 10.55 mg/L) and cancer of the oesophagus in Linxien, while a more recent study (Zhang *et al*., 2003) reported a concentration of 19.6 mg/L nitrate-N in well water in the county of Cixian, an area where mortality from oesophageal cancer was very high. These studies reported nitrate levels higher than the level (8 mg/L) in Chichen county, a low-risk area for oesophageal cancer.

Table 2.1. Ecological studies of ingested nitrate and nitrite and the risk for stomach and oesophageal cancer

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Asia					
China					
Wang *et al.* (1979), 49 production brigades, Linxien County	Oesophagus (150)	Incidence, 1969–76	Nitrate in wells 1976–77, 4 seasons	Correlation (summer), $r = 0.233$; P-value < 0.05	Average concentration of nitrates, 10.56 mg/L
Zhang *et al.* (1984), 6 high-risk and 4 low-risk districts	Stomach (151)	Mortality ($\times 10^{-5}$): high risk (range), 31–113, low risk (range), 7–12	**Nitrate and nitrite in gastric juice; 809 (high risk) and 554 (low risk) subjects** Nitrate Nitrite	**High- versus low-risk areas (mg/mL)** 24.3 versus 30.9 ($P < 0.01$) 0.27 versus 0.10 ($P < 0.001$)	Concentrations are medians; subjects were patients with chronic stomach complaints.
Lu *et al.* (1986), Linxian (high-risk area) and Fanxian (low-risk area) counties	Oesophagus (150)	Mortality, 1978; rate $\times 10^{-5}$, men: Linxian, 151; Fanxian, 35	**Nitrate in 24 h-urine, 1982, healthy subjects (148 high risk, 96 low risk)** High-risk area Low-risk area	 94 mg 48 mg P-value = 0.001	Nitrate levels are median in mg/person/day.

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Wu *et al.* (1993), 69 counties from 25 provinces	Stomach (151), oesophagus (150)	Mortality, 1975–75; cumulative rates, 0–64 years	**Nitrate in 12-h urine, 1982, healthy subjects (about 30 per xiang[a], 2 xiangs per county)**	**Correlation coefficient**	Nitrate was significantly associated (positive correlation) with tumours of nasopharynx and liver and leukaemia.
			Stomach	$r = -0.14$ (NS)	
			Oesophagus	$r = -0.10$ (NS)	
Lin *et al.* (2003), Lufeng County (low-risk area), Nan'ao County (high-risk area)	Oesophagus (150)	Mortality, age-adjusted rate ($\times 10^{-5}$); 10 (Lufeng); 110 (Nan'ao)	**Nitrate in 12-h urine (nmol/g creatinine), 120 healthy persons per county**		Daily intake of nitrate also higher in high-risk area; period to which mortality rates and urinary measurements refer not reported
			High-risk area	7.1	
			Low-risk area	3.1	
				P-value = 0.01	
Zhang *et al.* (2003), Cixian County (high-risk area), Chichen County (low-risk area)	Oesophagus (150)	Mortality, 1974–76 rate ($\times 10^{-5}$) men: Cixian, 147.7; Chichen, 8.3	**Nitrite and nitrate in well water, 1993–96 (33 in Cixian, 31 in Chichen; mg/L nitrogen), 1996**	**Cixian versus Chichen**	Rates adjusted for Chinese population; similar results for years 1993–95
			Nitrate	19.6 versus 8.0 ($P < 0.01$)	
			Nitrite	0.01 versus 0.002 ($P < 0.01$)	

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Japan					
Kamiyama *et al.* (1987), Akita (high-risk area), Iwate (low-risk area) Prefectures	Stomach (151)	Mortality, 1969–78; rate $\times 10^{-5}$, men: Akita, 33, Iwate, 101	**Nitrate in 24-h urine, 104 healthy subjects, 1983** High-risk area Low-risk area	 116 mg 140 mg *P*-value = 0.07	Nitrate levels are median in mg/person/day.
Tsugane *et al.* (1992), Yokote, Saku (high-risk areas), Ninohe, Ishikawa (low-risk areas) cities	Stomach (151)	Mortality, 1985–87; rate, men ($\times 10^{-5}$): high-risk, 49, 43; low-risk, 30, 17	**Nitrate in 24-h urine, 134 adults, 40–49 years, 1989–90** High-risk area Low-risk area	*Mean nitrate (mg/day/person)* 120–166 167–203	Age-adjusted mortality (world population)

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Europe					
Denmark					
Jensen (1982), towns of Aalborg and Aarhus and other towns in northern Jutland	Stomach (151), oesophagus (150)	Incidence (1968–72) from the Danish Cancer Registry	**Nitrate in drinking-water (mg/L) in 1976**	**Incidence ($\times 10^{-5}$)**	Incidence adjusted for age using European population; for stomach cancer, similar results for 5-year periods 1943–47 and 1963–67
			Stomach		
			Men		
			Aalborg: 27.1	41.5	
			Aarhus: 0.2	28.4	
			Women		
			Aalborg: 27.1	21.8	
			Aarhus: 0.2	13.2	
			P-value	> 0.0001	
			Oesophagus		
			Men		
			Aalborg: 27.1	5.6	
			Aarhus: 0.2	4.1	
			Women		
			Aalborg: 27.1	2.0	
			Aarhus: 0.2	2.4	
			P-value	NS	

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results		Comments
Eastern Europe						
Zemla & Kolosza (1979), Zabrze, cities of Maciejov, Mikulczyce (low-nitrate and-nitrite districts) and Grzybowice, Pawlow (high-nitrate districts), Poland	Stomach (151)	Incidence, 1965–75	**Mean level in drinking-water (mg/L)** *Low (0.076–0.125)* Nitrate Nitrite *High (0.365–0.699)* Nitrate Nitrite	**Incidence rates (× 10^{-5})** *Men* *Women* 11.9 3.7 13.4 9.6 36.8 NR 52.6 4.8		Age-standardized rates, population of Zabrze; all rates but one significantly different from the city mean; no differences for women
Juhasz *et al.* (1980), 230 communities in Szabolcs-Szatmar county, Hungary	Stomach (151)	Incidence, 1975	**Nitrate in drinking-water** > 100 mg/L < 100 mg/L	**No. of communities ≥ 20 × 10^{-5}/ Total No. of communities** 127/205 12/25 Prevalence ratio, 1.29 (NS)		Prevalence ratio (proportion of communities with nitrate >100 mg/L divided by the proportion of communities with nitrate <100 mg/L); source of rates and period of nitrate measurement not stated
Zatonski *et al.* (1989), town of Opole (low risk), and Swierczow and Domaszowice rural areas (high risk), Poland	Stomach (151)	Mortality, 1980–84	**Urinary nitrate (24 h) from 50 (low-risk town) and 47 (high-risk areas) subjects** Low-risk areas High-risk areas	**Nitrate excretion (median, mg/day)** 76 106 $P = 0.0072$		Age-adjusted rates

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Sandor *et al*. (2001), 192 communities of the county of Baranya, Hungary	Stomach (151)	Mortality, 1984–93; SMR	**Nitrate in drinking-water (mg/L), 1974–93** < 80 > 80	**SMR (95% CI)** 0.96 (0.79–1.13) 1.42 (1.25–1.58) Correlation: 0.59 (P = 0.072)	Expected deaths from national rates; correlation significant if nitrate log-transformed
Gulis *et al.* (2002), 60 villages in the district of Trnava, Slovakia	Stomach (151)	Incidence (1986–95) from the National Cancer Registry; SIR	**Nitrate in drinking–water (mg/L), 1975–95** 0–10 10–20 > 20	**SIR (95% CI)** 0.96 (0.71–1.30) 0.87 (0.69–1.10) 1.08 (0.87–1.35)	Expected cases calculated from the district rates
Italy					
Gilli *et al.* (1984), 1199 communities of the Piemonte region	Stomach (151)	Incidence (1976–79) from the Tumour Register of Piemonte and hospital releases; SIR	**Nitrate in drinking-water (recent years)** > 20 mg/L < 20 mg/L	**No. of communities with** SIR **significantly high/Total No. of communities** Relative Risk (95% CI) 10/155 1.0 (reference) 5/1059 13.7 (3.4–60.0)	Expected cases from regional rates (Piemonte)

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Knight *et al.* (1990), Cagliari, Verona (low risk), Siena, Arezzo (high risk) cities	Stomach (151)	Mortality, 1976–80; age, 35–64 years	**Salivary nitrate and nitrite (nmol/mL) from hospital visitors (187 low-risk areas, 144 high-risk areas)** *Nitrate* Low-risk areas High-risk areas *Nitrite* Low-risk areas High-risk areas	 88.3 65.5 $P = 0.094$ 101.4 82.4 $P = 0.082$	Rates standardized to the world population; concentrations are geometric means.
Knight *et al.* (1992), urban areas of Florence (high-risk) and Cagliari (low-risk)	Stomach (151)	Mortality, 1980–92; age, 0–74 years	**Urinary nitrate from healthy subjects (39 in low-risk areas, 40 in high-risk areas)** *Nitrate (mg/12 h)* Cagliari (low-risk area) Florence (high-risk area) *Rate ($\times 10^{-5}$)* Men Cagliari Florence	 33.7 37.1 $P = 0.55$ 15.6 27.2	Rates standardized to the entire Italian population; concentrations are geometric means.

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Spain					
Sanz Anquela *et al.* (1989), 9 areas (230 municipalities) of the province of Soria	Stomach (151)	Mortality and incidence, 1977–86	**Nitrate in drinking-water (mg/L) (1986)** Men Mortality Incidence	**Correlation coefficient** $r = 0.825$ ($P < 0.01$) $r = 0.701$ ($P < 0.05$)	Age- and sex-adjusted, overall province as standard population; incidence from pathology reports
Morales-Suárez-Varela *et al.* (1995), 258 municipalities of the province of Valencia	Stomach (151)	Mortality, 1975–80	**Nitrate in drinking-water (1968)** *Men* < 25 mg/L 25–50 mg/L > 50 mg/L *Women* < 25 mg/L 25–50 mg/L > 50 mg/L	**Rate ($\times 10^{-5}$)** 21.3 16.7 28.9 16.5 13.2 19.0	Significant differences for level >50 mg/L compared with <25 mg/L only for the age group 55–75 years (both men and women)

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
United Kingdom					
Hill *et al.* (1973), Worksop and 9 neighbouring 'control' towns	Stomach (151)	Mortality, 1963–71; SMR	Nitrate in drinking-water: Worksop, 93 mg/L; control towns, 15 mg/L	SMR, 1.27 ($P < 0.05$); all SMRs but one NS	Expected deaths calculated from national rates
Davies (1980), Nottinghamshire: 5 mining towns (including Worksop) and 4 non-mining towns	Stomach (151)	Mortality, 1958–75; SMR	*Men* Worksop Mining towns Non-mining towns *Women* Worksop Mining towns Non-mining towns	**SMR** 0.97 (*P*-value, NS) 0.92 (*P*-value, NS) 0.91 ($P < 0.5$) 1.23 (*P*-value, NS) 1.04 (*P*-value, NS) 0.86 ($P < 0.5$)	Expected deaths from national rates; populations in 1961 and 1971 plus adjustment for social class and mining

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Fraser & Chilvers (1981), 32 rural districts of Anglia and Yorkshire	Stomach (151)	Mortality, 1969–73 and 1974–78; SMR	**Nitrate in drinking-water**	**SMR (1974–78)**	Expected deaths from national rates of population in 1971
			Men		
			Anglia		
			< 25 mg/L	0.90 ($P < 0.05$)	
			25–50 mg/L	1.07 ($P < 0.05$)	
			> 50 mg/L	1.29 ($P<0.05$)	
			Yorkshire		
			< 25 mg/L	0.99 ($P < 0.05$)	
			25–50 mg/L	1.05 ($P < 0.05$)	
			> 50 mg/L	NR	
			Women		
			Anglia		
			< 25 mg/L	1.00 ($P < 0.05$)	
			25–50 mg/L	0.98 ($P < 0.05$)	
			> 50 mg/L	1.05 ($P < 0.05$)	
			Yorkshire		
			< 25 mg/L	0.88 ($P < 0.05$)	
			25–50 mg/L	1.40 ($P < 0.05$)	
			> 50 mg/L	NR	
Beresford (1985), 229 urban areas of England, Scotland and Wales	Stomach (151)	Mortality, 1969–73; SMR	**Nitrate in drinking-water (1971) as mg/L nitrogen**	**Regression coefficient (SMR for a each mg/L)**	Expected deaths from national rates, population in 1971; results adjusted for social class.
			Men	–1.19 ($P < 0.05$)	
			Women	–2.02 ($P < 0.01$)	

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Forman *et al.* (1985), Wales and Northeast (high risk), Oxford and Southeast (low risk)	Stomach (151)	Mortality, 1981; SMR	**Salivary nitrate and nitrite from selected subjects in each region (fasting samples)** *Nitrate (nmol/mL)* Low risk High risk *P*-value *Nitrite (nmol/mL)* Low risk High risk *P*-value	**SMR** Low risk, 0.59–0.91 High risk, 1.12–1.62 169 92.5 < 0.05 80.8 44.7 < 0.05	Fasting samples; similar results for both sexes and social class
Barrett *et al.* (1998), 148 water supply zones in Yorkshire	Stomach (151), oesophagus (150)	Incidence (1975–94) from the Yorkshire Cancer Registry	**Nitrate in drinking-water (average 1990–95)** *Stomach* Quartile 1, 2.4 mg/L Quartile 2, 5.0 mg/L Quartile 3, 13.7 mg/L Quartile 4, 29.8 mg/L *Oesophagus* Quartile 1, 2.4 mg/L Quartile 2, 5.0 mg/L Quartile 3, 13.7 mg/L Quartile 4, 29.8 mg/L	**Rate ratio (95% CI)** 1.00 1.02 (0.98–1.07) 0.86 (0.82–0.90) 0.91 (0.87–0.95) 1.00 1.01 (0.93–1.09) 1.01 (0.94–1.09) 1.06 (0.96–1.14)	Rates adjusted by age, sex, socioeconomic status and population density

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
North America					
Geleperin *et al.* (1976), Illinois, USA	Oesophagus (150)	Mortality, 1959–66; whites	**Nitrate in drinking-water** *Men* < 10 mg/L 40–45 mg/L, spring only > 40 mg/L, constant *Women* < 10 mg/L 40–45 mg/L, spring only > 40 mg/L, constant	**Rate ($\times 10^{-5}$)** 43.0 40.3 38.4 6.0 4.2 15.3	All comparisons NS
Van Leeuwen *et al.* (1999), 40 ecodistricts of Ontario, Canada	Stomach (151)	Incidence (1987–91) from the Ontario Cancer Registry	Nitrate in drinking-water (mg/L), 1987–91	Regression coefficient for ln(nitrate), b = –0.136 (–0.151, –0.122)	Age-standardized rates; results shown are for men.
South and Central America					
Cuello *et al.* (1976), several municipalities of the department of Nariño, Colombia	Stomach (151)	Incidence, 1968–72; 261 incident cases and 269 matched controls	**Nitrate in 173 water sources; nitrate and nitrite in urine and saliva of 282 subjects** Low-risk area High-risk area	**Nitrate (mg/L)** 1.7–14.6 12.5–39.0 (test not given) No differences in salivary nitrite	Level of risk by the case:control ratio in each area compared with the whole department

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
Zaldívar & Wetterstrand (1978), 25 provinces of Chile	Stomach (151)	Mortality (mean of 1960, 1962 and 1964)	**Nitrate in drinking-water (as mg/L nitrogen), 1953–75** Men Women	**Correlation coefficient** $r = 0.0335$ (NS) $r = 0.0486$ (NS)	Age-adjusted rates $\times 10^{-5}$
Armijo *et al.* (1981), Chillán, Linares (high risk), Antofagasta and Punta Arenas (low risk), Chile	Stomach (151)	Mortality	Nitrate in urine and saliva of 243 children aged 11–13 years (1977–80)	Antofagasta had significantly higher mean of urinary nitrate; no differences for nitrite in saliva	Actual values for concentration not provided, only graph and results of the test
Sierra *et al.* (1993), communities of Turrubares (high risk) and Hojancha (low risk), Costa Rica	Stomach (151)	Incidence (age-adjusted rate $\times 10^{-5}$): 66.1 (high risk), 26.8 (low risk)	**Nitrate in urine of children** Low-risk area ($n = 25$) High-risk area ($n = 26$)	**Nitrate (mmol/12 h)** 0.20 0.23 ($P = 0.75$)	Median: urinary nitrate excretion

Table 2.1 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure	Main results	Comments
International					
Hartman (1983), 12 countries (10 European, USA, Japan)	Stomach (151)	Mortality, 1974–75, adjusted rates ($\times 10^{-5}$)	Estimates of nitrate intake (mmol/day), 1970s	Correlation, $r = 0.88$	Correlation improved when nitrate-squared was used as a covariate.
Joossens *et al.* (1996), 24 countries	Stomach (151)	Mortality, (1984, 1986, 1987 or 1988), 45–74 years	**Nitrate in 24h urine 1986–87, 3303 adults aged 20–59 years** Men Women	**Correlation** $r = 0.63$ ($P = 0.001$) $r = 0.56$ ($P < 0.05$)	Age-adjusted rates, $\times 10^{-5}$, nitrate in mmol/day

CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; NS, not significant; SIR, standardized incidence ratio; SMR, standardized mortality ratio

[a] Formerly called communes

Europe

Denmark

In Denmark, Jensen (1982) compared the incidence of cancer at several sites in the towns of Aalborg and Aarhus, which were known to have high and low levels of nitrate in the water (27.1 and 0.2 mg/L, respectively). Significantly higher rates of stomach cancer were reported for the high-nitrate area (Aalborg), but no differences were seen for oesophageal cancer.

Eastern Europe

In Poland (Zemła & Kolosza, 1979), significantly higher incidence rates of stomach cancer among men were observed in districts of the town of Zabrze that had higher levels of nitrate in the drinking-water.

In Hungary, a positive but non-significant association between the incidence of stomach cancer and the level of nitrate in the water was reported for the county of Szalbolcs-Szatmar (Juhasz *et al*., 1980), and a non-significant correlation between the level of nitrate in the water and mortality from stomach cancer was found in 192 communities of the county of Banya (Sandor *et al*., 2001); however, in the latter study, there was a significantly increased standardized mortality ratio (SMR) of 1.42 for communities that had concentrations of nitrate greater than 80 mg/L.

Gulis *et al*. (2002) analysed the incidence of stomach cancer in 60 villages in the district of Trnava, Slovakia. The number of observed cases from 1986 to 1995 was retrieved from the national cancer registry and expected cases were calculated for each village using the age-and sex-specific rates for the whole district. No association was observed between incidence rates of stomach cancer and levels of nitrate in the drinking-water. The villages were grouped into three categories according to levels of nitrate (0–10 mg/L, 10–20 mg/L and > 20 mg/L); standardized incidence ratios (SIRs) for the three groups were close to unity and none was significant.

Italy and Spain

A strong positive association was also observed between the incidence of stomach cancer and the level of nitrate in the drinking-water in the Piemonte area, Italy (Gilli *et al*., 1984).

The relationship between nitrate in the drinking-water and the risk for stomach cancer was also assessed in two studies in Spain. In the province of Soria (Sanz Anquela *et al*., 1989), a high-risk area for stomach cancer, a significant positive correlation was observed with both mortality ($r = 0.83$) and incidence ($r = 0.70$), while no clear pattern was observed in the analysis of 258 municipalities of Valencia (Morales-Suárez-Varela *et al*., 1995).

United Kingdom

Several studies compared indicators of the occurrence of stomach cancer with the concentration of nitrate in the drinking-water in defined geographical areas with a high degree of variability in exposure, ranging from 2.4 mg/L nitrate in some areas of Yorkshire to 93 mg/L in a town in Nottinghamshire. An early report showed a significant

increase in mortality from stomach cancer (standardized mortality ratio (SMR), 1.27; $P < 0.05$) in Worksop, a town that had high levels of nitrate (93 mg/L) in the drinking-water (Hill *et al*., 1973), but not in control towns where levels of nitrate were lower (15 mg/L). However, a re-analysis of mortality in the same area (Davies, 1980) calculated expected deaths using SMRs standardized by social class and occupational group at the national level and also using the proportion of subjects in each community by social class and occupation in mining. No increase in mortality was found when mining activity and social class were taken into account. A trend towards higher SMRs for stomach cancer with increasing level of nitrate in the drinking-water was observed in rural districts of Anglia and Yorkshire (Fraser & Chilvers, 1981) (although most estimates were not significant) while a significant inverse relationship was estimated in the analysis of 229 urban areas of England, Wales and Scotland (Beresford, 1985). Barrett *et al*. (1998) conducted a study in Yorkshire, where cancer incidence was available from a regional cancer registry. Ecological assignment was carried out by mean levels of nitrate in tap-water (148 water supply zones, average levels of monthly measurements in 1990–95) and some other variables (socioeconomic status, population density), while individual variables (age and sex) were available from the cancer registry (1975–94) for subjects who were diagnosed with tumours of the stomach (15 554), oesophagus (5399) and brain (3441). For each tumour site, the expected number of cases for each water supply zone, sex and age group was calculated and Poisson regression was employed to model the potential effects of levels of nitrate on incidence rates. For stomach cancer, a significant reduction in risk was found for the third (relative risk, 0.86; 95% confidence interval [CI], 0.82–0.90) and fourth quartile (relative risk, 0.91; 95% CI, 0.87–0.95), while no association was observed for cancer of the oesophagus. [Levels of nitrate in this region were modest: only 0.3% (31/9333) of samples contained > 50 mg/L, and 16% of water supply zones had average levels > 25 mg/L)].

North America

In the USA, Geleperin *et al*. (1976) did not find significant differences in mortality from cancer of the oesophagus with levels of nitrate in the drinking-water in Illinois.

Van Leeuwen *et al*. (1999) conducted an ecological study in 40 ecodistricts of Ontario, Canada. Levels of nitrate in groundwater were assessed for each district using regional data from the monitoring system for municipal water supplies, and sex- and age-standardized cancer rates for stomach and several other cancer sites were calculated from data from the population-based cancer registry (1987–91). Regression analysis weighted by population size was used to examine the correlation between levels of nitrate and incidence of cancer. A significant inverse association was reported between the incidence of stomach cancer and level of nitrate in the drinking-water among men.

South America

The risk for stomach cancer in relation to nitrate was investigated in Nariño, a department located in the South of Colombia (Cuello *et al*., 1976); two areas were defined

within the department based upon the differential distribution of subjects in a case–control study. Concentrations of nitrate in wells and artesian waters from the high-risk area (13–39 mg/L) were much higher than those in the low-risk area (1.7–15 mg/L), although no formal tests were provided.

Following a previous report that showed a strong positive relationship between mortality from stomach cancer and the use of nitrate fertilizers (Zaldivar, 1977), a correlation study was undertaken in Chile that compared mortality from stomach cancer and levels of nitrate in the drinking-water in 25 provinces (Zaldívar & Wetterstrand, 1978); no association was found; non-significant correlation coefficients were 0.03 and 0.05 for men and women, respectively.

(ii) *Biomarkers of nitrate*

Asia

Two Japanese studies compared excretion of nitrate in 24-h urine samples from subjects selected in areas of low and high risk for mortality from stomach cancer. Kamiyama *et al*. (1987) observed lower levels of urinary nitrate in the prefecture of Akita, an area where mortality from stomach cancer was high, compared with the low-risk area of Iwate: median levels of excretion of nitrate were 116 and 140 mg per day per person, respectively ($P = 0.07$). No association was observed for urinary nitrate in the high-mortality areas of Yakote and Saku cities compared with the low-risk areas of Ninohe and Ishikawa cities (Tsugane *et al*., 1992).

In China, Zhang et al. (1984) analysed levels of nitrate in the fasting gastric juice of subjects from six areas where mortality from stomach cancer was high and four where it was low and showed an inverse significant association. [However, this study was carried out among patients with chronic stomach complaints.] Three studies in China used excretion of nitrate in urine samples as an indicator of exposure. Wu et al. (1993) compared urinary nitrate in healthy subjects and mortality rates from 69 counties in 25 Chinese provinces and found inverse non-significant associations with mortality from both cancer of the stomach ($r = –0.14$) and cancer of the oesophagus ($r = –0.10$). Lu et al. (1986) had previously reported an excretion of 94 mg nitrate per person per day in Linxian County (an area that had the highest mortality from cancer of the oesophagus), which was significantly higher than the level of 48 mg measured in Fanxian county, an area that had much lower mortality. A very similar result was reported in a more recent study (Lin et al., 2003): the level of urinary nitrate was 7.1 nmol/g creatinine in subjects from Nan'ao county, a high-risk area, which was more than twice that measured in Lufeng county (3.1 nmol/g), where mortality from cancer of the oesophagus was much lower.

Europe

In Poland, Zatonski *et al*. (1989) reported higher levels of urinary nitrate in subjects from rural areas where mortality from stomach cancer was high compared with residents in the town of Opole that had lower mortality from stomach cancer.

In Italy, lower levels of nitrate in the saliva were found in subjects from regions with high mortality from stomach cancer (Siena, Arezzo) compared with those from Cagliari and Verona, where mortality rates were lower, although the differences did not reach statistical significance (Knight *et al*., 1990). In another Italian study, no differences were found in levels of urinary nitrate measured in children in Florence and Cagliari, areas with high and low mortality from stomach cancer, respectively (Knight *et al*., 1992).

Forman *et al*. (1985) compared concentrations of nitrate in the saliva of subjects from areas where mortality from stomach cancer was high (Northeast and Wales) with those from subjects in low-risk areas (Southeast and Oxford) and found an inverse relationship, with significantly higher levels of nitrate in areas that had lower mortality from stomach cancer.

South and Central America

Armijo *et al*. (1981) compared levels of nitrate in the urine and saliva of children aged 11–13 years from four cities in Chile, two with high (Chillán, Linares) and two with low mortality rates (Antofagasta, Punta Arenas) for stomach cancer. Children in the two areas with lower mortality had the highest and the lowest mean levels of urinary nitrate; however, children from only one of the low-risk areas (Antofagasta) had significantly higher urinary excretion of nitrate in pairwise comparisons with the other three areas.

In a study in Costa Rica (Sierra *et al*., 1993), children from two areas with high and low incidence rates of stomach cancer had similar levels of urinary excretion of nitrate.

International

In the multinational INTERSALT study (Joossens *et al*., 1996), the mortality rates for stomach cancer were compared with excretion of nitrate in 24-h urine samples from 24 countries; significant correlations of 0.63 and 0.56 were observed for men and women, respectively. Although the source of data to estimate average intake of nitrate at the country level was not specified, a review by Hartman (1983) reported a correlation of 0.88 between the mortality rates from stomach cancer and the average intake of nitrate in 12 countries.

(b) Cohort studies (Table 2.2)

The Netherlands Cohort Study is a prospective study of diet, other lifestyle characteristics and the risk for cancer that was started in September 1986 and initially included 58 279 men and 62 573 women aged 55–69 years at recruitment (van Loon *et al*., 1997, 1998). Usual diet was assessed by means of a 150-item semiquantitative food-frequency questionnaire. Intake of nitrates was estimated using data from the databank of contaminants in foods from the State Institute for Quality Control of Agricultural Products (RIKILT, Wageningen). Information on water intake was combined with data from all waterworks in the country to determine the concentration of nitrate in the drinking-water for each home address by postal code. A case–cohort approach was used for data analysis: a subcohort of 3500 subjects was randomly sampled and followed every

Table 2.2. Cohort studies of ingested nitrate and nitrite and the risk for stomach and oesophageal cancer

Reference, location, name of study	Organ site (ICD code)	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
van Loon *et al.* (1998), Netherlands, The Netherlands Cohort Study	Stomach (151)	Cohort of 58 279 men and 62 573 women, 55–69 years; prospective follow-up September 1986–December 1992 by regional cancer registries and national pathology register; case–cohort analysis of 282 incident cases (219 men, 63 women) and 3123 subcohort members (1525 men, 1598 women)	Self-administered 150-item food-frequency questionnaire; food composition and nitrate in drinking-water from databank on contaminants in food (nitrate) and a food composition database (nitrite)	**Total nitrate, quintile (mean, mg/day)**		**Rate ratio**	Age, sex, smoking, education. coffee, vitamin C, β-carotene, family history of stomach cancer, prevalence of stomach disorders, use of refrigerator or freezer	Similar results after exclusion of subjects with stomach disorders or those diagnosed during the first year
				I (59.8)	63	1.00 (reference)		
				II (84.7)	67	1.25 (0.84–1.86)		
				III (104.4)	42	0.74 (0.47–1.15)		
				IV (127.3)	54	0.92 (0.59–1.44)		
				V (179.8)	56	0.90 (0.53–1.55)		
						P trend = 0.30		
				Nitrate from drinking-water (mean, mg/day)				
				Q1 (0.02)	61	1.00 (reference)		
				Q2 (1.65)	54	0.93 (0.62–1.39)		
				Q3 (3.85)	53	0.87 (0.51–1.31)		
				Q4 (6.91)	57	0.83 (0.55–1.24)		
				Q5 (16.5)	57	0.88 (0.59–1.32)		
						P trend = 0.39		
				Nitrate from foods (mean, mg/day)				
				Q1 (55.8)	69	1.00 (reference)		
				Q2 (79.4)	61	1.02 (0.69–1.51)		
				Q3 (98.7)	45	0.71 (0.46–1.09)		
				Q4 (120.7)	49	0.80 (0.51–1.25)		
				Q5 (172.2)	58	0.80 (0.47–1.37)		
						P trend = 0.18		
				Total nitrite, quintile (mean, mg/day)				
				I (0.01)	47	1.00 (reference)		
				II (0.04)	51	1.20 (0.78–1.86)		
				III (0.09)	58	1.18 (0.77–1.82)		
				IV (0.16)	46	0.88 (0.56–1.37)		
				V (0.35)	80	1.44 (0.95–2.18)		
						P trend = 0.24		

Table 2.2. (contd)

Reference, location, name of study	Organ site (ICD code)	Cohort description	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Knekt *et al.* (1999), Finland, several regions	Stomach (151)	9985 subjects, part of a multiphasic screening examination (the Mobile Health Clinic of the Social Insurance Institution); follow-up 1967–90 through nationwide Finish Cancer Registry; 68 incident cases of stomach cancer (43 men, 25 women)	Dietary history interview, referred to previous year	*Nitrate* Q1 Q2 Q3 Q4 *Nitrite* Q1 Q2 Q3 Q4	Not given	1.00 (reference) 1.01 (0.56–1.84) 0.52 (0.25–1.08) 0.56 (0.27–1.18) *P* trend = 0.09 1.00 (reference) 1.10 (0.58–2.11) 1.88 (1.01–3.49) 0.71 (0.28–1.78) *P* trend = 0.90	Age, sex, municipality, smoking, energy intake	No association with NDMA for stomach cancer; mean daily intake: 77 mg nitrate (92% from vegetables); 5.3 mg nitrite (94% from cured meats and sausages)

CI, confidence interval; ICD, International Classification of Diseases; NDMA, *N*-nitrosodimethylamine; Q, quartile

2 years for vital status and record linkage with all regional cancer registries. During a follow-up period of 6.3 years (up to December 1992), 347 cases of stomach cancer were identified. After exclusion of prevalent cases and those not microscopically confirmed or having incomplete dietary information, the analysis was carried out on 282 cases (219 men and 63 women) and 3123 subcohort members (1525 men and 1598 women). Total mean intake of nitrate in the subcohort was 111 mg per day (105 mg from food, 5.8 mg from drinking-water). No significant inverse associations were found for total nitrate intake, intake of nitrate from foods or intake of nitrate from water after adjustment for several factors including vitamin C intake. An analysis that excluded subjects with stomach disorders or those who were diagnosed during the first year did not modify these patterns substantially.

During 1966–72, a multiphasic screening examination was undertaken in several regions of Finland by the Mobile Health Clinic of the Social Insurance Institution. As part of the main study, data on food consumption were collected from 9985 individuals (5274 men and 4711 women) who had never had cancer (Knekt *et al*., 1999). Dietary information was collected by means of an interview, and several food composition databases were used to calculate intake of nitrate. During a 24-year period (1967–90), 68 cases of cancer of the stomach were ascertained through the Finnish Cancer Registry. A non-significant inverse association was observed for nitrate intake: compared with the first quartile, relative risks for the second, third and fourth quartiles of dietary nitrate were 1.01, 0.52 and 0.56, respectively, none of which was significant. All of these estimates were adjusted for age, sex, municipality, tobacco smoking and energy intake.

(c) Case–control studies (Table 2.3)

Several case–control studies have analysed the relationship between the occurrence of tumours of the stomach or oesophagus and intake of nitrate from foods, but very few provided separate estimates for the intake of nitrate from drinking-water. Most of these studies were carried out in populations who had relatively low levels of nitrate in the drinking-water and the majority of ingested nitrate was provided by diet.

China

One case–control study from Taiwan, China (Yang *et al*., 1998) was designed to assess the relationship between levels of nitrate in the drinking-water and mortality from stomach cancer. Information on the levels of calcium, magnesium and nitrate in the drinking-water were available from the Taiwan, China Water Supply Corporation for 252 of 361 municipalities. Cases were 6766 registered deaths from stomach cancer in residents from these municipalities from 1987 to 1991; age- and sex-matched controls were selected from among deaths from other causes excluding gastrointestinal disorders, cardiovascular diseases and some tumours. Levels of nitrate measured in 1970 in water in the municipality of residence was used as an indicator of exposure. No association was observed between mortality from stomach cancer and levels of nitrate in the drinking-water

Table 2.3. Case–control studies of ingested nitrate and nitrite and the risk for stomach and oesophageal cancers

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
China									
Yang *et al.* (1998), China (Province of Taiwan), 1987–91	Stomach (151)	6766 (4480 men, 2286 women) deaths from 1987 to 1991 obtained from the Bureau of Vital Status, residents in 252 (of 361) municipalities of the Province of Taiwan	6766 selected among deaths from other causes, excluding those associated with gastrointestinal problems, cardiovascular and cerebrovascular diseases and tumours of the bladder, prostate, lung, oesophagus, head and neck	Levels of nitrate in each municipality's treated drinking- water supply for the year 1990, from the Taiwan Water Supply Corporation	**Nitrate-N from drinking water, tertiles (mg/L) range (median)** < 0.22 (0.04) 0.23–0.44 (0.37) ≥ 0.45 (0.67) *P* for trend	 2109 2126 2531	 1.00 0.95 (0.87–1.03) 1.02 (0.93–1.11) 0.44	Age, sex, year of death	Significant inverse association with magnesium and calcium in drinking-water; relative risks for nitrate (tertiles) adjusted for calcium and magnesium: 1.10 (1.00–1.20) and 1.14 (1.04–1.25)

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Europe									
Buiatti *et al.* (1990), 4 areas in northern and central Italy, 1985–87	Stomach (151)	1016 (640 men, 376 women) aged 75 years or under from all hospitals in the areas of study; 100% histologically confirmed; participation rate, 83%	1159 population controls from municipal lists of residents; stratified by age, sex according to distribution of cases; participation rate, 81%	Interviewer-administered structured questionnaire of 146 food items; Italian and British FCTs	**Nitrate, quintiles (mean, mg/day)** 1 (53) 2 (81) 3 (103) 4 (130) 5 (193) *P* for trend **Nitrite, quintiles (mean, mg/day)** 1 (2.1) 2 (2.8) 3 (3.4) 4 (4.1) 5 (5.9) *P* for trend	 NR NR 	 1.0 (reference) 0.9 (0.7–1.1) 0.9 (0.6–1.1) 0.7 (0.5–0.9) 0.9 (0.7–1.2) [0.68] 1.0 (reference) 1.0 (0.8–1.4) 1.2 (0.9–1.7) 1.4 (1.0–2.0) 1.9 (1.3–2.7 [0.005]	Age, sex, area, urban/rural residence, migration from south, socioeconomic status, familial history of stomach cancer, body mass index, total energy intake	Interaction between antioxidant nutrients (vitamin C plus α-tocopherol) and nitrosating/ nitrosable compounds (protein plus nitrite)

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Boeing *et al.* (1991), Southeast Bavaria and Hesse, Germany, 1985–87	Stomach (151)	143 (50% men, 50% women) aged 32–80 years from five main hospitals in the two areas; 100% histologically confirmed; participation rate, 85%	579 in total; 328 hospital controls plus 251 visitor controls selected from the same hospitals as the cases; participation rate, 90% for hospital controls; unknown for visitors	Interviewer-administered questionnaire of 74 food items; German FCT	**Nitrate, quintiles (mg/day)** 1 (53) 2 (81) 3 (103) 4 (130) 5 (193) *P* for trend	NR	1.00 (reference) 0.93 (0.53–1.64) 0.61 (0.32–1.19) 0.61 (0.30–1.27) 1.26 (0.59–2.70) [1.0]	Age, sex, hospital, vitamin C, carotene, calcium	Both control groups were pooled in this analysis; having well-water supply (supposed high nitrate contents) had a relative risk of 2.26 (1.19–4.28) compared with having central water supply.
González *et al.* (1994), five provinces in northern and central Spain, 1988–89	Stomach (151)	354 (235 men, 119 women) aged 31–88 years from 15 public hospital, residents in the study areas; 100% histologically confirmed; participation rate, 100%	354 admitted to the same hospitals as the cases; individually matched by age (± 3 years), sex, area of residence	Interviewer administered diet history, structured by meals; English and Spanish FCTs	**Nitrate, quartiles (mg/day)** 1 (< 84) 2 (84–146) 3 (145–234) 4 (> 234) *P* for trend **Nitrite, quartiles (mg/day)** 1 (< 1.3) 2 (1.4–1.8) 3 (1.9–2. 4) 4 (> 2.4) *P* for trend	NR NR	1.00 0.80 (NR) 0.65 (NR) 0.45 (NR) 0.007 1.00 1.20 (NR) 1.09 (NR) 1.28 (NR) 0.38	Age, sex, area of residence, total caloric intake	CIs not provided; in this study a significant increased risk was observed with higher intake of NDMA; significant interaction between nitrosamines and vitamin C.

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hansson *et al.* (1994), five counties in central and northern Sweden, 1989–92	Stomach (151)	338 (sex distribution not given) aged 40–79 years resident in the study areas; 100% histologically confirmed; participation rate, 74%	679 randomly sampled from a population register in the areas of study; stratified by age, sex according to the distribution of the cases; participation rate, 77%	Interviewer administered FFQ of 45 items referred to adolescence and 20 years prior to interview; Swedish FCT	**Quartiles (Q; 20 years prior to the interview)** *Nitrate* Q4 versus Q1 *P* for trend *Nitrite* Q4 versus Q1	 NR NR 	 0.55 (0.38–0.80) 0.002 1.22 (0.82–1.81)	Age, sex	Mean intake of nitrate (controls), 42 mg/day
La Vecchia *et al.* (1994, 1997), Milan area, Italy, 1985–92	Stomach (151)	723 (443 men, 280 women) aged 19–74 years from four largest teaching and general hospitals; 100% histologically confirmed; participation rate, 95%	2024 (1189 men, 835 women) admitted to the same hospitals (excluding neoplastic and digestive wards); participation rate, 95%	Interviewer-administered FFQ of 29 items; Italian FCT	**Nitrate, quintiles (mg/day)** 1 (< 63) 2 (63–80) 3 (81–96) 4 (97–116) 5 (> 116) *P* for trend **Nitrite, quintiles (mg/day)** 1 (< 1.91) 2 (1.92–2.41) 3 (2.42–2.94) 4 (2.95–3.64) 5 (> 3.64) *P* for trend **Nitrite (mg/day)** < 2.7 ≥ 2.7	 228 156 117 117 105 123 128 126 153 193 NR 	 1.00 (reference) 0.64 (0.49–0.83) 0.50 (0.38–0.67) 0.52 (0.39–0.70) 0.43 (0.32–0.59) < 0.001 1.00 (reference) 0.98 (0.72–1.33) 0.99 (0.72–1.36) 1.15 (0.84–1.59) 1.35 (0.96–1.88) < 0.05 1.00 (reference) 1.44 (1.2–1.7)	Age, sex, education, family history of stomach cancer, body mass index, energy intake	Combined effect of nitrite with methonine high/high versus low/low, 2.45 (1.9–3.2)

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Pobel *et al.* (1995), Marseilles, France, 1985–88	Stomach (151)	92 (59 men, 33 women; mean age, 67 years) from 8 major centres for gastric surgery in Marseilles; 100% histologically confirmed; participation rate, 100%	128 hospital (74 men, 54 women) controls from two specialized centres for re-education for trauma or injuries; stratified by age, sex according to the distribution of the cases; participation rate, 100%	Interviewer-administered diet history, structured by meals; French FCT	**Nitrate, tertiles** 1 2 3 *P* for trend **Nitrite, tertiles** 1 2 3 *P* for trend	 NR NR 	 1.00 0.49 (0.24–1.01) 0.76 (0.38–1.50) 0.96 1.0 0.83 (0.41–1.67) 0.88 (0.44–1.79) 0.49	Age, sex, occupation, total energy intake	Mean intake of nitrate (controls), 143 mg/day; no significant association with nitrate from different sources; a significant increased risk was observed with higher intake of NDMA.

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Palli *et al.* (2001), Florence, 1985–87	Stomach (151)	382 (239 men, 143 women) aged 75 years or under from hospitals in the area of study; 100% histologically confirmed	561 population controls from municipal lists of residents; stratified by age, sex according to distribution of cases	Interviewer-administered structured questionnaire of 146 food items; Italian FCT	**Nitrate, tertiles (mean, mg/day)** 1 (62.6) 2 (93.2) 3 (107.4) *P* for trend **Nitrite, tertiles (mean, mg/day)** 1 (2.5) 2 (3.5) 3 (5.4) *P* for trend	NR NR 	1.0 (reference) 0.7 (0.5–1.0) 0.6 (0.4–0.9) 0.01 1.0 (reference) 1.4 (1.0–2.0) 1.4 (1.0–2.0) 0.04	Age, sex, urban/rural residence, social class, familial history of stomach cancer, body mass index, total energy intake	Estimates not adjusted for other dietary factors; a stepwise procedure retained only total protein, β-carotene and α-tocopherol intake as associated with risk for stomach cancer; no association with DMA or NDMA

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North America									
Risch *et al.* (1985), Newfoundland, Manitoba and Toronto, Canada, 1979–82	Stomach (151)	246 (163 men, 83 women) aged 35–79 years from the province tumour registries (Newfound-land, Manitoba) or pathology reports of 21 hospitals in Toronto; 100% histologically confirmed; participation rate, 44%	246 population controls from provincial electoral lists or municipal lists of residents; individually matched to cases by age (within 4 years), sex, province of residence; participation rate, 58%	Interviewer-administered diet history; FCT from the USDA and other sources	Nitrate, per 100 mg/day Nitrite, per 1 mg/day	NR NR	0.66 (0.54–0.81) 1.71 (1.24–2.37)	Age, sex, province of residence (matched analysis), total food consumption, ethnicity	No association with NDMA
Rademacher *et al.* (1992), Wisconsin, USA, 1982–85	Stomach (151)	1268 (758 men, 510 women) deaths from stomach cancer in the Wisconsin Bureau of Health Statistics	1268 randomly selected from all other deaths (excluded other gastrointestinal problems); matched for sex, year of birth, year of death	Recorded levels of nitrate in municipal water sources (1970 edition) and those measured in private wells (data not provided)	**Level of nitrate-N (mg/L)** > 0.5 versus ≤ 0.5 > 2.5 versus ≤ 25 > 5.0 versus ≤ 5 > 10.0 versus < 10 Private wells versus public	 207 113 25 6	 0.92 (0.75–1.12) 0.97 (0.74–1.35) 0.86 (0.69–1.08) 1.50 (0.12–18.25) 1.09 (0.82–1.47)	Age, sex (matched analysis)	Nitrate-N in private wells was significantly higher than that in public supplies.

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Rogers *et al.* (1995), three counties of Washington State, USA, 1983–87	Oesophagus (150)	645 upper aero-digestive tract cancers identified through the Cancer Surveillance System (SEER Program), of which 127 were oesophageal tumours (94 men, 33 women); participation rate, 67%	458 from random-digit dialling in the three counties; frequency-matched by sex, age (5-year interval)	Self-administered FFQ of 125 food items; food composition from report of the National Academy of Sciences	**Nitrate, tertiles (mg/day)** 1 (< 134) 2 (134–226) 3 (> 226) *P* for trend *High vitamin C* 1 (< 134) 2 (134–226) 3 (> 226) *Low vitamin C* 1 (< 134) 2 (134–226) 3 (> 226) **Nitrite, tertiles (mg/day)** 1 (< 1.06) 2 (1.06–1.60) 3 (> 1.60) *P* for trend *High vitamin C* 1 (< 1.06) 2 (1.06–1.60) 3 (> 1.60) *Low vitamin C* 1 (< 1.06) 2 (1.06–1.60) 3 (> 1.60)	 33 39 25 NR NR 26 28 43 NR NR 	 1.00 (reference) 0.71 (0.38–1.33) 0.44 (0.24–0.93) 0.078 1.00 (reference) 0.73 (NR) 0.44 (NR) 1.63 (NR) 1.44 (NR) 1.27 (NR) 1.00 (reference) 1.17 (0.57–2.38) 1.58 (0.73–3.44) 0.20 1.00 (reference) 2.24 (NR) 1.49 (NR) 2.93 (NR) 2.23 (NR) 5.07 ($P < 0.05$)	Age, sex, pack–years of cigarettes, drink–years of alcohol, energy intake, vitamin C, body mass index, level of education	Interaction between nitrite and vitamin C (NS); slightly increased risk (NS) for intake of NDMA; high NDMA with low vitamin C had a significantly increased risk versus low NDMA and high vitamin C.

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mayne *et al.* (2001); Engel *et al.* (2003), Connecticut, Washington state, New Jersey, USA, 1993–95	Stomach (151), cardia and non-cardia; oesophagus (150), SCC, ADC	Stomach: 255 cardia (217 men, 38 women), 352 non-cardia (244 men, 108 women); oesophagus: 282 ADC (235 men, 47 women), 206 SCC (166 men, 40 women) aged 30–79 years from three population-based tumour registries; 100% histologically confirmed; participation rate, 72% (overall)	687 from random-digit dialling and Health Care Finance Administration rosters: frequency-matched by age (5-year group), sex, geographic area; participation rate, 70%	Interviewer-administered FFQ of 104 items; FCT from the University of Minnesota and other databases	Nitrite, 75th percentile compared with 25th percentile	NR	*Oesophagus* SCC 1.13 (0.82–1.56) ADC 1.05 (0.80–1.38) *Stomach* Non-cardia 1.65 (1.26–2.15) Cardia 1.05 (0.79–1.40)	Age, sex, area (matching), race, proxy status, income, education, body mass index, cigarettes/day, years of consumption of beer, wine and liquor, sodium, energy intake	Interview with proxies for 30% of cases and 3.4% of controls

Table 2.3 (contd)

Reference, study location, study period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mayne *et al.* (2001); Engel *et al.* (2003) (contd)		Stomach: 368 non-cardia	695 controls	Interviewer	**Nitrite, quartiles** 1 2 3 4 2–4 **High vitamin C** Low nitrite High nitrite **Low vitamin C** Low nitrite High nitrite	NR	 1.0 1.5 (1.0–2.4) 1.8 (1.1–3.0) 2.5 (1.4–4.3) 1.7 (1.1–2.6) 1.0 (reference) 2.10 (1.36–3.25) 2.25 (1.46–3.47) 2.95 (1.90–4.59)	Age, sex, area, race, respondent type, income, energy intake, smoking status, history of gastric ulcer	Levels (quartiles) of nitrite intake among controls by sex: men: 1.7–5.8, 5.9–7.5, 7.6–9.9, 10.0–39.2; women: 1.9–5.3, 5.4–6.9, 7.0–9.1, 9.2–31.2; increased risk of oesophageal ADC, SCC and stomach cardia cancer with low vitamin C intake (regardless of nitrite intake) compared with high vitamin C and low nitrite intakes

ADC, adenocarcinoma; CI, confidence interval; DMA, dimethylamine; FCT, food composition table; FFQ, food-frequency questionnaire; ICD, International Classification of Diseases; NDMA, *N*-nitrosodimethylamine; NR, not reported; NS, not significant; SCC, squamous-cell carcinoma; USDA, US Department of Agriculture

However, a weak but significant association was seen after adjustment for levels of calcium and magnesium in the water.

Europe

A large case–control study was carried out in Italy (Buiatti *et al*., 1990) based on 1016 cases and 1159 controls from two areas at high risk for stomach cancer (Florence–Siena and Forlí–Cremona–Imola) and two at low risk (Genoa and Cagliari). Dietary intake of nitrate (mg per/day) was derived from personal interviews using a structured questionnaire of 146 items and data on nitrate content in foods were obtained from Italian and British food composition tables. The association with risk for stomach cancer was assessed through the distribution of nitrate controls to define quintiles, taking the lowest as the reference category, and by means of a model that included age, sex, social class, familial history of stomach cancer and caloric intake. No association was found between dietary intake of nitrate and the risk for stomach cancer. Palli *et al*. (2001) updated the results of Buiatti *et al*. (1990) on the cases from the local cancer registry of Florence by expanding the series of controls and applying an updated Italian food composition table. Overall, this re-analysis included 382 cases and 561 controls. There was a significant reduction in risk for stomach cancer with increasing nitrate intake (P for trend = 0.01). [The authors stated that the effect of nitrate disappeared when adjustment was made for protein (associated with increased risk), and β-carotene and α-tocopherol (associated with protection against risk). However, adjusted estimates were not provided.]

Boeing *et al*. (1991) carried out a hospital-based case–control study in Southeastern Bavaria and Hesse (Germany). A total of 143 cases and 579 controls (patients and visitors) were interviewed using a standard questionnaire of 74 items coupled with a German food composition table to obtain dietary intake of nitrate. Information on the type of water supply for each residence was also collected. No association was observed between the risk for stomach cancer and quintiles of dietary intake of nitrate, adjusted for age, sex, hospital, vitamin C, carotene and calcium. Residence with a well-water supply was associated with an increased risk for stomach cancer (relative risk, 2.26; 95% CI, 1.19–4.28) compared with a central water supply. [The authors stated that private well-waters were supposed to have a higher content of nitrate, but information on levels of nitrate in water was not available for the areas under study.]

Another hospital-based case–control study that included 354 cases and 354 matched controls (González *et al*., 1994) was carried out in five provinces of Spain (Barcelona, La Coruña, Lugo, Soria and Zaragoza). A diet history method administered personally by a trained interviewer was used to assess habitual diet during a typical week of the year before the diagnosis (cases) or interview (controls); Spanish and British food composition tables were used to estimate the intake of nutrients. In the matched analysis (age, sex, area), an inverse association between risk for stomach cancer and increasing quartiles of nitrate intake was observed with a significant trend (P for trend = 0.007) after also adjusting for total caloric intake. The effect was more evident when the analysis was restricted to cases with diffuse-type histology.

Hansson *et al*. (1994) reported the results of a case–control study in Sweden. A food frequency questionnaire was administered by an interviewer to 338 cases of stomach cancer and 679 population controls who were identified through the population register; information on usual diet during adolescence and the 20 years before the interview was collected and nitrate intake was calculated from a Swedish food composition table. The highest quartile of nitrate intake, adjusted for sex and age, was significantly associated with decreased risk for cancer of the stomach (odds ratio, 0.55; 95% CI, 0.38–0.80; *P* for trend = 0.002). However, no association was observed when dietary intake of nitrate was further adjusted for vitamin C and α-tocopherol. [A plausible interpretation of such results could be that the decrease in risk is probably due to the inhibitory effect on nitrosation of vitamin C and vitamin E.]

A hospital-based case–control study carried out in Italy included 723 cases and 2024 controls selected from the four largest teaching hospitals from the Greater Milan area (La Vecchia *et al*., 1994, 1997). An interviewer administered a 29-item food-frequency questionnaire and an Italian food composition table was used to assess the usual dietary intake of nitrate. In a multivariate analysis that took into account potential dietary and non-dietary confounders, the highest quintile of nitrate consumption showed a significant reduction in the risk for stomach cancer (relative risk, 0.43; 95% CI, 0.32–0.59; based on 105 exposed cases; *P* for trend < 0.001) compared with the lowest quintile.

A hospital-based case–control study that included 92 cases and 128 controls was carried out in the area of Marseilles, France (Pobel *et al*., 1995). A questionnaire on diet history was administered by an interviewer at the hospital and a French food composition table was used to estimate the intake of nitrates. No association was observed between intake of nitrate and the risk for stomach cancer overall or when different dietary sources were considered separately, while a significant increase in risk was reported for the dietary intake of preformed nitrosamines. [Potential limitations of this study are the small sample size and the fact that controls were selected in two specialized medical centres of re-education for trauma or injuries, which may not provide a good representation of the dietary habits of the study base.]

North America

The first case–control study on risk for stomach cancer that reported results for dietary intake of nitrates was a Canadian study by Risch *et al*. (1985). Overall 246 cases of stomach cancer were identified from the cancer registries of two provinces of Canada and from the pathology reports of hospitals in Toronto; individually matched controls were selected from provincial or municipal lists of residents. Usual diet was assessed by the diet history method administered by an interviewer and nutrient intakes were calculated using a food composition table from the USA and other sources. The matched analysis with further adjustment for ethnicity showed a significant reduction in risk for stomach cancer for each 100 mg nitrate ingested per day (odds ratio, 0.66; 95% CI, 0.54–0.81). However, the effect of nitrate totally disappeared when adjustment was made for intake of vitamin C from vegetables.

Rademacher *et al*. (1992) reported a case–control study based upon death certificates to assess the association of stomach cancer with nitrate in the drinking-water. Cases were 1268 deaths from stomach cancer from 1982 to 1985 in Wisconsin (USA) and matched controls were selected from among deaths from causes other than gastrointestinal problems. Levels of nitrate recorded in 1970 for municipal sources or measured in private wells were used as indicators of exposure at the residence of the subject at the time of death. Using several cut-off points to define exposure, no significant associations between nitrate in drinking-water and mortality from stomach cancer were observed. [The authors noted that the levels of nitrate in private wells were measured at the time of the study, which was about 20 years later than those recorded for public sources.]

Only one study has evaluated the potential association between dietary intake of nitrate and oesophageal cancer. Rogers *et al*. (1995) conducted a population-based case–control study in Washington State (USA) of 645 tumours of the upper aerodigestive tract, that included 125 oesophageal cancers, which were identified through the cancer surveillance system and 458 frequency-matched controls. A self-administered, 125-item food-frequency questionnaire and a food composition table from the National Academy of Sciences were used to estimate the usual intake of nitrate. High consumption (> 226 mg per day) was significantly associated with a decrease in the risk for cancer of the oesophagus compared with lowest intake (< 134 mg per day) after adjustment for potential non-dietary and dietary confounders (including vitamin C intake).

2.2.2 *Ingested nitrite*

(a) Ecological studies

Most ecological studies that addressed tumours of the stomach or oesophagus focused mainly on the intake of nitrates whereas nitrite was rarely assessed. The main features and results of ecological studies on the relationship between intake of nitrite and tumours of the stomach or oesophagus are summarized in Table 2.1.

China

In China, Zhang *et al*. (1984) analysed levels of nitrite in the fasting gastric juice of subjects from six areas where mortality from stomach cancer was high and from four areas with low mortality rates and showed a significant positive association for nitrite.

The only ecological study that assessed the association between intake of nitrite and oesophageal tumours was carried out in China. Zhang *et al*. (2003) observed a significantly higher level of nitrite in well-water in the county of Cixian (0.01 mg/L), an area where mortality from oesophageal cancer is very high, compared with the low-risk county of Chichen (0.002 mg/L).

Europe

In a study in Italy (Knight *et al*., 1990), lower levels of nitrite in saliva were found in subjects from regions where mortality from stomach cancer was high (Siena, Arezzo)

compared with subjects from Cagliari and Verona, where rates were lower, although the differences did not reach statistical significance.

Only one study assessed measured levels of nitrite in the drinking-water in relation to stomach cancer. In Poland, Zemła and Kolosza (1979) reported a significantly higher incidence of stomach cancer among men in districts of the town of Zabrze that had higher levels of nitrite in the drinking-water.

In the United Kingdom, Forman *et al*. (1985) compared levels of nitrite in saliva in subjects from an area where mortality from stomach cancer was high (Northeast and Wales) with those from low-risk areas (Southeast and Oxford) and found an inverse relationship; levels were significantly higher in areas with lower mortality.

South America

The risk for stomach cancer in relation to ingested nitrite was investigated in the department of Nariño, Colombia (Cuello *et al*., 1976). No differences in levels of salivary nitrite were seen between two areas of high or low risk. Armijo *et al*. (1981) carried out a study in children aged 11–13 years from four provinces in Chile, two of which had high and two of which had low mortality rates for stomach cancer. No differences were observed in the concentrations of nitrite in saliva gathered from these children.

(b) Cohort studies

Two cohort studies (described in detail in Section 2.2.1(*b*)) analysed the association between ingested nitrite and the risk for cancers of the stomach or oesophagus; their main findings are summarized in Table 2.2.

In the Netherlands Cohort Study (van Loon *et al*., 1997, 1998), intake of nitrite was estimated using the database on food composition values from the Nutrition and Food Research Institute (TNO, Zeist). The association between stomach cancer and intake of nitrite, adjusted for age and sex, was not clear and did not show a clear dose–response relationship. The only significant estimate was for the fifth quintile of intake (age- and sex-adjusted relative risk, 1.49; 95% CI, 1.01–2.20), which became non-significant (relative risk, 1.44; 95% CI, 0.95–2.18) after simultaneous adjustment for vitamin C, β-carotene, level of education, tobacco smoking and use of a refrigerator or freezer. [The decreased risk after adjustment for vitamin C and β-carotene could reflect the potential inhibitory effect on nitrosation of such nutrients. The possible interaction between nitrite intake and vitamin C was not assessed; no data on dietary intake of nitrosamines were provided in this study.]

The Mobile Health Clinic of the Social Insurance Institution in Finland (Knekt *et al*., 1999) collected data on food consumption by means of a diet history interview, and several food composition databases were used to calculate intake of nitrite. After a 24-year follow-up (1967–90), 68 cases of cancer of the stomach were identified. Dietary intake of nitrite was not associated with risk for stomach cancer after adjustment for age, sex, municipality, tobacco smoking and energy intake.

(c) Case–control studies

The findings of case–control studies on the risk for stomach cancer and oesophageal cancer in relation to ingested nitrites are summarized in Table 2.3. Most studies that addressed nitrite intake also considered nitrate and have thus been described in full in Section 2.2.1(*c*). Only the few studies that addressed exclusively intake of nitrite are described in detail here.

Europe

A large case–control study that included 1016 cases of stomach cancer and 1159 controls was carried out in Italy (Buiatti *et al*., 1990). Nitrite intake (mg per day) was derived from personal interview using a structured questionnaire of 146 items and the application of food composition tables from Italian and English sources. The association with risk for stomach cancer was adjusted for age, sex, social class, familial history of stomach cancer, body mass index and caloric intake. There was a significant increase in risk with increasing levels (quintiles) of nitrite intake (P for trend = 0.005). Furthermore, an interaction was observed between antioxidants (vitamin C and α-tocopherol) and protein and nitrites: cases and controls were classified into three categories (low, medium, high) according to these two groups of compounds. Using the low/low category as the reference, the odds ratio for the high antioxidants/low protein and nitrite category was 0.4, while that for the low antioxidant/high protein and nitrite category was 2.1 (a fivefold difference in relative risk for the two extreme categories). Palli *et al*. (2001) updated the results of Buiatti *et al*. (1990) for the cases from Florence by expanding the series of controls and applying an updated Italian food composition table that included values for dimethylamine and *N*-nitrosodimethylamine (NDMA). Similarly to the previous study, a significant positive association with nitrite was observed (P for trend = 0.04); a positive association was also observed with estimated intakes of dimethylamine and NDMA.

Another Italian case–control study carried out in the four largest teaching hospitals of the Greater Milan area (La Vecchia *et al*., 1994, 1997) assessed nitrite intake through a 29-item food-frequency questionnaire and an Italian food composition table. A significant trend for an increased risk for stomach cancer was observed with higher intake of nitrite (categorized in quartiles), although none of estimates was statistically significant (P for trend < 0.05); however, when two levels of nitrite intake were considered in relation to the median (≥ 2.7 versus < 2.7 mg per day), a significant increased risk was observed (odds ratio, 1.44; 95% CI, 1.2–1.7). In this study, methionine was associated with an increased risk for stomach cancer and the combined effect of both compounds was assessed; the odds ratio for the category with high intake of nitrite and methionine was 2.45 (95% CI, 1.9–3.2) compared with the category with lowest consumption for both compounds.

A hospital-based case–control study of stomach cancer in four provinces of Spain (González *et al*., 1994) used a diet history method and Spanish and British food composition tables to estimate intake of nutrients. In the matched analysis of 354 pairs, a slightly increased risk for high intake of nitrite was observed, although the trend was not significant; the effect of nitrite was only evident for tumours of the intestinal type, while

no effect or inverse risk estimates were observed for diffuse-type tumours of the stomach. [In this study, there was a significant association with NDMA (results not provided) and an interaction with vitamin C: subjects who had a high intake of nitrosamines and a low intake of vitamin C had an odds ratio of 1.98 (95% CI, 1.3–3.1) compared with those who had a low vitamin C and low nitrosamine intake.]

Hansson *et al*. (1994) reported the results of a case–control study in Sweden of 338 cases of stomach cancer and 679 controls. Nitrite intake was calculated from a food-frequency questionnaire and the Swedish food composition table. The age- and sex-adjusted relative risk for the highest quartile of nitrite intake compared with the lowest quartile was 1.22 (95% CI, 0.82–1.81).

A hospital-based case–control study carried out in the area of Marseilles, France (Pobel *et al*., 1995) used a diet history questionnaire combined with a French food composition table to estimate the intake of nitrites. No association was observed in relation to risk for stomach cancer overall or when different dietary sources of nitrite (from vegetables or other foods) were considered separately. [Potential limitations of this study are described in Section 2.2.1(*c*).]

North America

Risch *et al*. (1985) reported the results from a population-based case–control study in two provinces of Canada and the area of Toronto. Usual diet was assessed by the diet history method which was administered by an interviewer and nutrient intakes were calculated using a food composition table from the USA and other sources. The matched analysis with adjustment for ethnicity and total caloric intake showed a significant increase in risk for stomach cancer for every milligram of nitrite consumed per day (odds ratio, 1.71; 95% CI, 1.24–2.37). [No adjustment was made for β-carotene, although this nutrient was also found to be associated with a decreased risk for stomach cancer. The interaction between intake of nitrite and antioxidant micronutrients was not assessed.]

Two case–control studies from the USA addressed the association of nitrite intake with the risk for oesophageal cancer alone or with tumours at other sites. Rogers *et al*. (1995) conducted a population-based study in Washington State and used a 125-item food-frequency questionnaire and a food composition table from the National Academy of Sciences to estimate the usual intake of nitrite. A positive but non-significant association was observed. Although no statistically significant interactions were found, the data suggested that individuals with both low intake of vitamin C and high nitrite intake had a higher risk for oesophageal cancer (odds ratio, 5.07; $P < 0.05$). [In this study, the pattern of estimates for NDMA was very similar to that reported for nitrites yielding a positive trend (P for trend = 0.06), although estimates for tertiles of intake were not statistically significant. There was a suggestion of an interaction of NDMA with vitamin C: those with higher tertiles of NDMA and low vitamin C intake had a three-fold significantly increased risk of oesophageal cancer ($P < 0.05$).]

A more recent population-based case–control study in the USA (Mayne *et al*., 2001) considered stomach and oesophageal tumours according to their localization or

histological type. Overall, 1095 cases were identified through population cancer registries; 458 frequency-matched controls were selected by random-digit dialling. Personal interviews were obtained using a 104-item food-frequency questionnaire and dietary data were linked to published databases on nitrite content. Separate results were provided for 352 non-cardia stomach cancers, 225 tumours located in the cardia, 206 squamous-cell type tumours of the oesophagus and 282 oesophageal adenocarcinomas. Adjusted for several potential confounders including total energy intake (but no nutrients), high intake of nitrite was significantly associated with an increased risk for non-cardia stomach cancer only. However, compared with persons with low nitrite and high vitamin C intakes, persons with low vitamin C intake had a significantly increased risk for cancers of the stomach (cardia and non-cardia) and oesophagus (adenocarcinomas and squamous-cell carcinomas). Intake of nitrite was further examined in cases of cardia stomach cancer from this study using categorization by quartiles according to the consumption of controls (Engel *et al*., 2003). A significant increase in risk was found for all levels of intake compared with the lowest.

2.2.3 *Preneoplastic lesions*

Superficial gastritis, chronic atrophic gastritis, intestinal metaplasia and dysplasia have been postulated to be part of the sequential process that leads to stomach carcinoma, and are therefore considered to be precursor lesions. The roles of nitrate, nitrite and nitrosation have been investigated in relation to this process, mainly in some areas in Colombia that are at high-risk for stomach cancer. In the Nariño area, a cohort of subjects was recruited between 1973 and 1983, all of whom had a gastroscopy and biopsy at baseline. Cross-sectional analysis of the first biopsy was carried out for 1670 subjects (Correa *et al*., 1990a). Taking normal mucosa as the reference category, positive versus negative level of nitrite in gastric juice (above or below the median) gave the following age-adjusted odds ratios: hyperplasia, 4.3; atrophy, 6.5; metaplasia, 8.3; and dysplasia, 16.8 (overall $P < 0.0001$); the corresponding values for nitrate (> 24 versus ≤ 24 mg/L) were 1.4, 1.8, 2.1 and 2.7 (P for trend < 0.0001). However, stomach nitrite failed to predict future changes in the same end-points (Correa *et al*., 1990b). Within this cohort, a further analysis was carried out for 263 subjects, including 117 cases of stomach cancer and 146 controls [not specified] (Chen *et al*., 1990). Odds ratios for the presence of nitrite in gastric juice and the risk for precursor lesions compared with subjects with normal mucosa, adjusted for age, sex, pH, sodium/creatinine ratio and addition of salt, were: superficial gastritis, 2.99 (95% CI, 0.88–10.17); chronic atrophic gastritis, 3.49 (95% CI, 0.84–14.40); intestinal metaplasia, 4.39 (95% CI, 1.36–14.16); and dysplasia, 24.72 (95% CI, 1.97–309.64). In the same region, Cuello *et al*. (1979) characterized the histopathology of stomach biopsies from 123 patients in a village of the department of Nariño, in the Andean region of Colombia. Measurable levels of nitrite in gastric juice were detected in patients who had chronic atrophic gastritis but not in those who had superficial gastritis or normal mucosa; the level was significantly elevated (4.2 mg/L;

$P < 0.01$) only among those who had intestinal metaplasia with dysplasia. There were no differences in the level of nitrate.

During 1989–90, a gastroscopic screening survey was carried out in a rural area of the province of Shandong (China), which has one of the highest rates of stomach cancer (You *et al*., 1996). Endoscopic biopsies, fasting gastric juice and overnight urine were collected; data were available for 583 persons (312 men and 271 women). The level of nitrite in gastric juice was above the detection level for 7% of subjects with superficial/chronic atrophic gastritis versus 17% of those with intestinal metaplasia ($P < 0.01$). Furthermore, among those with detectable values, the geometric mean gastric content of nitrite was 0.8 ng/mL for subjects with intestinal metaplasia compared with 0.4 ng/mL for those with superficial/chronic atrophic gastritis ($P = 0.06$). This pattern was similar for subjects whose gastric juice had a pH > 2.4, but not for the subgroup that had a lower pH. On the contrary, the level of nitrate in urine was higher among subjects who had superficial/chronic atrophic gastritis (281 ng/mL) than among those who had intestinal metaplasia (242 ng/mL), but the differences were non-significant.

2.3 Tumours of the brain

Epidemiological studies of brain cancer are challenging because of problems with the specificity of diagnosis and the difficulties of patients to recall past exposures while experiencing the effects of cerebral lesions, surgery or treatment. Numerous epidemiological studies have investigated the potential role of nitrate and nitrite in relation to the occurrence of central nervous system (mainly brain) tumours in adults and children. These were mostly case–control studies that estimated nitrate and nitrite consumption from either residential tap-water or other dietary sources and are summarized in Table 2.4.

In the studies that considered dietary exposure, participants, their mothers (childhood brain tumour studies) or proxy respondents (for deceased or disabled patients in some studies of adult brain tumours) were requested to recall consumption of selected foods; this information was then linked to data on the content of nitrate and nitrite in food. In each of the studies reviewed below, approximately 50 foods (range, 42–100) were included; in many, the authors stated that foods with a high content of nitrate, nitrite or *N*-nitroso compounds were intentionally well represented.

The studies that considered exposure from tap-water used past measures of nitrate in public utilities and/or measured nitrate and/or nitrite in newly collected water samples from the current home or the residence at the time of diagnosis. With the exception of one study (Ward *et al*., 2005), water testing relied on semiquantitative test strips.

As outlined in Section 2.1, studies were not reviewed if they only considered less direct potential indicators of exposure to nitrate and/or nitrite. However, the potential association between the consumption of cured meat and the occurrence of brain tumours has been studied extensively. Many studies suggested an association between brain tumours in children and consumption of cured meat by the mother during pregnancy and/or

Table 2.4. Case–control studies of nitrate and nitrite in the drinking-water and from dietary sources and the risk for adult and childhood central nervous system tumours

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Adult								
Australia								
Giles *et al.* (1994), Melbourne and other cities of Victoria, Australia, 1987–91	Glioma primary	409 cases (243 men, 166 women) from registry/ 14 hospitals, aged 20–70 years; 100% histologically confirmed; response rate, 66%; 409 controls (243 men, 166 women) randomly selected from electoral roll; matched by sex, age; history of stroke, epilepsy, prior brain tumour excluded; response rate, 45%	Mailed questionnaire (59 foods), followed by in-person interview, linked to published tables of food content; proxy for 54.3% of male cases, 3.3% of male controls, 50.6% of female cases and no female controls	**Nitrate in the diet** *Men* T1 T2 T3 *Women* T1 T2 T3 **Nitrite in the diet** *Men* T1 T2 T3 *Women* T1 T2 T3	 74 95 74 73 48 45 60 90 93 61 47 58	 1.0 1.42 (0.89–2.26) 1.13 (0.68–1.86) 1.0 0.48 (0.25–0.91) 0.53 (0.28–0.96) 1.0 1.58 (0.96–2.61) 1.58 (0.96–2.58) 1.0 0.77 (0.43–1.37) 0.98 (0.55–1.72)	Alcohol consumption, tobacco smoking	Period for which diet was ascertained was not specified; among men, most food groups and nutrients were above null, and no adjustment was made for total energy intake [in this particular study, the Working Group believed this adjustment should have been made because of misclassification, not because energy intake is a potential risk factor].

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Europe								
Boeing *et al.* (1993); Steindorf *et al.* (1994), Rhein–Neckar–Odenwald area, Germany, 1987–88	Brain, primary	226 cases (99 men, 127 women; 115 gliomas, 81 meningiomas, 30 acoustic neuromas) from 2 neurosurgery clinics, aged 25–75 years; 100% histologically confirmed; response rate, 97.8%; 418 controls (185 men, 233 women) from compulsory regional residential register; frequency-matched by sex, age; response rate, 72%	Diet: in-person questionnaire (42 foods, previous 5 years) linked to published tables of food content; proxy for 12% of cases, 3% of controls Water (test): semi-quantitative test strip estimation of tap-water at current home; available for 60.1% of cases and 90.4% of controls who had lived in the region > 1 year	**Nitrate in the diet** *Glioma* T1 T2 T3 *P* for trend **Nitrate in water (test)** Not detected 10 mg/L 25 mg/L 50–100 mg/L	 29 34 30 60 12 28 4	 1.0 (reference) 1.0 (0.6–1.8) 0.9 (0.5–1.5) 0.64 1.0 (reference) [0.5 (0.2–0.9)] [0.7 (0.4–1.2)] [0.3 (0.1–0.7)]	Age, sex, alcohol consumption, tobacco smoking Crude	Diet: odds ratios include 53 (23.5%) cases and no controls who did not live in the study region for at least 1 year since 1970 [approximately previous 17 years]. Water test: case water samples were sent to hospital, whereas control water samples were tested in home immediately after sample collection

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Boeing *et al.* (1993); Steindorf *et al.* (1994) (contd)			Water (records): residential history linked to measures in 1971–87 from 69 water providers, plus other data for 2% with private well/spring; attempted for subjects living in region >1 year since 1970, 76.6% of cases and 100% of controls; data available for 168 cases and 406 controls (97% of each attempted)	**Nitrate in water (records)** *(mean nitrate mg/L)* Q1 (0–2.0) Q2 (> 2.0–11.3) Q3 (> 11.3–25.2) Q4 (> 25.2) **Nitrite in the diet** *Glioma* T1 T2 T3 *P* for trend	 45 38 44 41 26 31 36	 1.0 (reference) 0.99 (0.60–1.63) 1.12 (0.69–1.83) 1.00 (0.61–1.64) 1.0 (reference) 1.1 (0.6–1.9) 1.1 (0.6–2.0) 0.62	Age, sex (diet, tobacco smoking, bottled water considered) Age, sex, alcohol consumption, tobacco smoking	Water records: mean nitrate levels were very similar for cases and controls during each year (1970–87); consideration of tumour type or latency period did not alter conclusions.
Israel								
Kaplan *et al.* (1997), Tel Hashomer/ central Israel, 1987–91	Brain tumour, primary malignant or benign	139 cases (mostly glioma and meningioma; 63 men, 76 women) from one medical centre, aged 18–75 years; 100% histologically confirmed; response rate, 77%; 278 controls (126 men, 152 women); matched by age, sex, ethnic origin (one friend, one orthopaedic patient per case); response rate not specified	Questionnaire (100 foods) for the period 10 years before diagnosis, linked to published tables of food content; proxy for 30% of each group	Nitrate or nitrite in the diet	NR	No association [no odds ratios reported]	Total energy intake, matching variables	Analyses repeated by tumour type, and for the two control groups separately in subanalyses

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
USA								
Blowers *et al.* (1997), Los Angeles County, CA, USA, 1986–88	Glioma	94 women from tumour registry (county resident), alive and well enough to provide an interview, aged 25–74 years; 100% histologically confirmed; response rate, 67%; 94 female county residents; matched on neighbourhood of residence (at case diagnosis), age, race (black/white); response rate, 72%	In-person questionnaire (43 foods, 90% estimated ascertainment of nitrate and nitrite); no proxies used; complete nutrient data available for 91 (97%) case–control pairs	**Nitrate in the diet**	NR		Total food intake, body mass index	Only surviving female cases were included and may lead to survivor bias; ethnicity, religion, education, vitamin intake, diabetes and allergies, asthma and eczema considered but not included in the final models.
				Q1		1.0		
				Q2		1.3 (0.5–3.3)		
				Q3		1.1 (0.4–2.7)		
				Q4		0.7 (0.2–1.8)		
				P for trend		0.46		
				Nitrite in the diet	NR			
				Q1		1.0		
				Q2		0.6 (0.2–1.3)		
				Q3		0.4 (0.1–1.0)		
				Q4		1.4 (0.6–3.5)		
				P for trend		0.55		
				Nitrite from cured meat	NR			
				Q1		1.0		
				Q2		0.9 (0.3–2.4)		
				Q3		1.3 (0.6–3.0)		
				Q4		2.1 (1.0–4.6)		
				P for trend		0.07		

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Lee *et al.* (1997), San Francisco Bay area, CA, USA, 1991–94	Glioma	494 cases (282 men, 212 women) from one cancer centre rapid-ascertainment system, aged > 20 years; 100% histologically confirmed; response rate, 82%; 462 controls (254 men, 208 women) from random-digit dialling; frequency-matched by age, sex, race/ethnicity (white, black, Asian, Hispanic, other)	Mailed questionnaire (79 foods, usual consumption in previous year) followed by in-person interview, linked to database of nutrients; 46% proxies for cases; available for 434 (94%) cases and 439 (99%) controls	**Nitrite with vitamin C**			Age, education, income	Analyses repeated to exclude proxy respondents: difference in nitrate intake became non-significant for women; increased risk in men with high nitrite and low vitamin C intake was not attenuated and remained significant; nitrite and vitamin C each dichotomized at the median.
				Men				
				Low nitrite, high vit C	36	1.0 (reference)		
				Low nitrite, low vit C	75	1.3 (0.7–2.3)		
				High nitrite, high vit C	58	1.0 (0.6–1.8)		
				High nitrite, low vit C	71	2.1 (1.1–3.8)		
				Women				
				Low nitrite, high vit C	24	1.0 (reference)		
				Low nitrite, low vit C	52	1.2 (0.6–2.4)		
				High nitrite, high vit C	69	1.6 (0.9–3.0)		
				High nitrite, low vit C	36	1.5 (0.7–3.1)		
						Mean weekly consumption (standard deviation)		
				Nitrate in the diet				
				Men				
				Cases		726.3 (26.8)		
				Controls		775.8 (26.3)		
				P-value		NS		
				Women				
				Cases		52.1 (22.8)		
				Controls		660.9 (41.2)		
				P-value		≤ 0.05		
				Nitrite in the diet				
				Men				
				Cases		6.5 (0.3)		
				Controls		6.0 (0.2)		
				P-value		NS		
				Women				
				Cases		4.9 (0.2)		
				Controls		4.6 (0.2)		
				P-value		NS		

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Schwartzbaum *et al.* (1999), Ohio, USA, 1993–96	Glioma	40 cases (19 men, 21 women) from 1 hospital network at time of first surgery for possible brain tumour; median age, 52.5 years; all white; 100% histologically confirmed; response rate, 95%; 48 controls (22 men, 26 women) from same hospital network (orthopaedic or gynecological surgery patients with no malignant neoplasm, diabetes, pregnancy, obesity, gastro intestinal disease, coronary heart disease or stroke); matched by age, sex; all white; response rate, 92%	Nitrite: diet questionnaires (prior year) translated to nutrients via software and published tables; no proxies Vitamins C and E: pre-surgery serum analysed; available for 23 (57.5%) cases	**Nitrite from cured meat (mg/day)**			Protein, fat, total calories, cured meat, body mass index	Nitrite intake from cured meats: median, 0.6 mg/day in cases; 0.3 mg/day in controls; exclusion criteria for controls probably resulted in a group with a different diet than population controls; odds ratios for nitrite intake above the median from individual types of cured meats at null or below. *low = < median values, high = ≥ median values
				Q1 (< 0.16)	9	1.0 (reference)		
				Q2 (0.16–0.39)	7	2.0 (NR)		
				Q3 (0.40–0.91)	14	2.2 (NR)		
				Q4 (≥ 0.92)	10	2.1 (NR)		
				P for trend		0.36		
				Nitrite-serum vitamin C				
				Low nitrite* low vit C	8	1.0 (reference)		
				Low nitrite high vit C	1	0.1 (0.0–1.2)		
				High nitrite, high vit C	2	0.7 (0.1–9.4)		
				High nitrite, low vit C	12	1.6 (0.3–8.0)		

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Chen *et al.* (2002); Ward *et al.* (2005), eastern Nebraska, USA, 1988–93	Glioma, primary	251 cases (139 men, 112 women) from cancer registry/11 hospitals in region, aged ≥ 21 years; all white; 100% histologically confirmed; response rate, 89% [among eligible]; 498 controls (283 men, 215 women) from a randomly selected control group (same base population) from a study of non-Hodgkin lymphoma (random-digit dialling, supplemented by Medicare records for age >65 years); frequency-matched on age, sex, vital status; all white; response rate, 71%	Diet: telephone questionnaire (48 food items), linked to published tables; available for 236 (94%) cases and 449 (90%) controls; proxies for 76% cases, 60% controls Public water: residence histories linked to nitrate water-quality monitoring data from 236 public water systems, 1947–85; available for 130 (52%) cases and 319 (64%) controls; ≥70% person–years after 1964 (when water data more complete); lag of 3–8 years between the exposure period and case diagnosis.	**Nitrate in the diet**			Energy, age, sex, farming, education, respondent, family history of central nervous system tumour	Subanalyses separate by respondent type, histological type (no meaningful differences); low statistical power to evaluate risk at public water system nitrate levels above 5–10 mg/L nitrate-N; only about 15% of cases and controls believed to be exposed to 10 mg/L nitrate-N in public water supplies >8 years. No interaction observed between vitamin C intake and dietary nitrite.
				Q1	59	1.0 (reference)		
				Q2	81	1.2 (0.7–1.9)		
				Q3	43	0.7 (0.4–1.2)		
				Q4	53	0.7 (0.4–1.2)		
				P for trend		0.1		
				Nitrate in water, public system, 1965–84 (Mean mg/L nitrate-N)			Age, sex, respondent, education, farming	
				Q1 (< 2.38)	24	1.0 (reference)		
				Q2 (2.38–2.57)	39	1.4 (0.7–2.7)		
				Q3 (2.58–4.32)	33	1.2 (0.6–2.3)		
				Q4 (> 4.32)	34	1.3 (0.7–2.6)		
				Nitrate with vitamin C				
				Q1/high vit C	8	1.0 (reference)	Birth year, sex, respondent, education, farming	
				Q2/high vit C	22	2.4 (0.8–6.9)		
				Q3/high vit C	13	2.0 (0.7–6.0)		
				Q4/high vit C	13	2.1 (0.7–6.4)		
				Q1/low vit C	15	2.3 (0.8–6.9)		
				Q2/low vit C	16	1.6 (0.5–4.8)		
				Q3/low vit C	17	1.7 (0.6–4.7)		
				Q4/low vit C	17	2.0 (0.7–5.8)		
				Years of nitrate ≥ 5 mg/L nitrate-N				
				0	22	1.0 (reference)	Birth year, sex, respondent, education, farming	
				1–4	62	1.3 (0.7–2.5)		
				5–9	20	1.8 (0.8–4.1)		
				≥ 10	26	1.1 (0.5–2.2)		

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Chen *et al.* (2002); Ward *et al.* (2005) (contd)			Private water: tap-water samples from well used in 1985, laboratory analysed; available for 47 cases and 43 controls (75% and 60%, respectively, of those who had used a private well in 1985)	**Years of nitrate ≥ 10 mg/L nitrate-N**			Energy, age, sex, farming, education, respondent, family history of central nervous system tumour	
				0	85	1.0 (reference)		
				1–8	25	1.1 (0.6–2.1)		
				≥ 9	20	1.1 (0.6–2.0)		
				Nitrate in water, private well				
				< 10 mg/L nitrate-N	40	1.0 (reference)		
				≥ 10 mg/L nitrate-N	7	1.2 (0.4–4.1)		
				Nitrite in the diet			Birth year, sex, respondent, education, farming, β-carotene, fibre, calories	Chen *et al.* (2002)
				Q1	66	1.0 (reference)		
				Q2	66	1.0 (0.6–1.7)		
				Q3	57	0.9 (0.5–1.5)		
				Q4	47	0.8 (0.5–1.3)		
				P for trend		0.3		
				Animal sources (mg/day)			Birth year, sex, respondent, education, farming, β-carotene, fibre, calories	Ward *et al.* (2005)
				Q1 (< 0.29)	29	1.0 (reference)		
				Q2 (0.29–< 0.46)	25	0.8 (0.4–1.7)		
				Q3 (0.46–0.63)	31	1.3 (0.6–2.7)		
				Q4 (≥ 0.63)	36	1.3 (0.6–2.9)		
				Plant sources (mg/day)				
				Q1 (< 0.31)	34	1.0 (reference)		
				Q2 (0.31–< 0.43)	29	1.0 (0.5–2.1)		
				Q3 (0.43–0.59)	28	3.2 (1.2–8.3)		
				Q4 (≥ 0.59)	30	2.8 (1.0–8.2)		
				Preformed dietary intake + endogenous nitrite from water nitrate (mg/day)				
				< 1.4	21	1.0 (reference)		
				1.4–< 2.1	43	1.8 (0.9–3.6)		
				2.1–< 3.3	28	1.1 (0.5–2.3)		
				≥ 3.3	28	1.1 (0.5–2.5)		

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Childhood								
Europe								
Cordier *et al.* (1994), Paris/Ile de France region, France, 1985–87	Intra-cranial tumour	75 cases (34 boys, 41 girls) from 13 hospitals in the region, aged 0–15 years, residents of Ile de France; 84% histologically confirmed; response rate, 69%; 113 controls (63 boys, 50 girls) from sample of residences in region, supplemented by telephone books; frequency-matched by birth year; response rate, 72%	Questionnaire (maternal diet during pregnancy) linked to French surveys and published tables of food content	**Nitrate in the diet** Q1 Q2 Q3 Q4 *P* for trend **Nitrite in the diet** Q1 Q2 Q3 Q4 *P* for trend	 NR NR NR NR NR NR 	 1.0 (reference) 1.5 (0.5–4.5) 0.5 (0.1–1.7) 1.5 (0.5–4.6) NS 1.0 (reference) 0.9 (0.3–2.7) 0.6 (0.2–2.3) 0.4 (0.1–0.4) NS	Age, sex, maternal age, maternal education	*N*-Nitroso compounds not considered; vitamin C non-significantly protective

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Israel								
Lubin *et al.* (2000), Israel; 1984–93	Central nervous system tumour, primary	300 cases (149 boys, 151 girls) from all neurosurgical departments in Israel drawn from the Jewish population only, aged 0–18 years; histological confirmation not specified; response rate, 81.7%; 574 controls (293 boys, 281 girls) from population registry; matched by sex, birth year, birth hospital (Israel) or country (outside Israel); response rate, 78.2%	Questionnaire (100 foods) during pregnancy and childhood linked to published tables of food content	**Nitrate in the diet** *Pregnancy* T1 T2 T3 *P* for trend *Childhood* T1 T2 T3 *P* for trend **Nitrite in the diet** *Pregnancy* T1 T2 T3 *P* for trend *Childhood* T1 T2 T3 *P* for trend	 NR NR NR NR NR NR NR NR NR NR NR NR 	 1.0 0.86 [NR] 1.15 (0.8–1.7) 0.43 1.0 0.84 [NR] 1.17 (0.8–1.7) 0.46 1.0 1.04 [NR] 0.97 (0.6–1.7) 0.91 1.0 0.86 [NR] 0.86 (0.5–1.6) 0.64	Total energy intake, matching variables	Not specified whether controls were drawn from the Jewish population only as were cases.

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
North America								
Bunin *et al.* (1993, 1994), Canada/USA, 1986–89	Brain tumours, PNET (1993), astrocytic glioma (1994)	321 cases with no previous malignancy from 33 paediatric oncology groups, aged <6 years; 166 (100 boys, 66 girls) PNET; 89% histologically confirmed; response rate, [77%]; 155 (81 boys, 74 girls) astrocytic glioma; 78% histologically confirmed; response rate, [74%]; 321 controls from random-digit dialing; matched on telephone area code + next 5 digits, birthdate (1 year), race (black/other); 166 PNET controls (90 boys, 76 girls); response rate, [73%]; 155 astrocytic glioma controls (85 boys, 70 girls); response rate, [74%]	Structured telephone interview (53 foods during pregnancy, 60–75% estimated ascertainment of nitrate and nitrite), linked to databases of portion size and food content	**Nitrate in the diet** *PNET* Q1 Q2 Q3 Q4 *P* for trend *Astrocytic glioma* Q1 Q2 Q3 Q4 *P* for trend **Nitrite in the diet** *PNET* Q1 Q2 Q3 Q4 *P* for trend *Astrocytic glioma* Q1 Q2 Q3 Q4 *P* for trend	 NR NR NR NR 40 32 38 34 NR NR NR NR 40 31 31 42 	 1.0 1.18 (0.64–2.19) 0.61 (0.34–1.09) 0.44 (0.23–0.84) 0.002 1.0 0.7 (0.3–1.4) 0.9 (0.4–1.8) 0.7 (0.3–1.4) 0.43 1.0 1.58 (0.79–3.16) 1.04 (0.57–1.89) 1.11 (0.58–2.10) 0.80 1.0 0.8 (0.4–1.6) 0.8 (0.4–1.5) 1.3 (0.7–2.6) 0.54	None (child diet, family income, maternal tobacco smoking considered) Family income None (child diet, family income, maternal tobacco smoking considered) Family income	Inverse PNET–nitrate association attenuated and became non-significant (p for trend = 0.19) after adjustment for other food components (vitamins A, C and E, folate, nitrite and nitrosamine) and vitamin/mineral supplements [only crude risk estimates provided in full].

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Preston-Martin *et al.* (1996); Pogoda & Preston-Martin (2001a,b), California (Los Angeles and San Francisco areas) and Washington (Seattle area) states, USA, 1984–91	Brain, cranial nerves, cranial meninges, primary	540 cases (298 boys, 242 girls) from 3 tumour registries, aged < 20 years, living in the study region at diagnosis in a home with a telephone; % histological confirmation not specified; response rate, [71%]; 801 controls (448 boys, 353 girls) from residents of the same counties and identified by random-digit dialling; frequency-matched by age, sex; response rate, [74%]	In-person questionnaire (47 foods, maternal intake during pregnancy), linked to published tables/software (1996 analyses) or year-specific nitrite levels from 26 food surveys of sodium nitrite levels (2001 analyses)	**Nitrite in the diet**			Age, sex, birth year, geographic area	No interaction with socioeconomic status (*p* for trend statistically significant for low and high socioeconomic groups); race and socioeconomic status considered but not included in final models.
				Q1	NR	1.0 (reference)		
				Q4	NR	1.1 (0.79–1.50)		
				[Other quartiles not reported]				
				Nitrite in vegetables only				
				Q1	NR	1.0 (reference)		
				Q4	NR	0.98 (0.71–1.3)		
				[Other quartiles not reported]				
				Nitrite in cured meat only (mg/day)				
				Q1 (<0.02)	122	1.0 (reference)		
				Q2 (0.02–0.29)	121	1.1 (0.78–1.5)		
				Q3 (0.30–1.28)	116	1.1 (0.78–1.5)		
				Q4 (> 1.28)	155	1.9 (1.3–2.6)		
				P for trend		0.003		
				Nitrite with prenatal vitamins supplements				
				Low nitrite/vit +	195	1.0 (reference)		Low nitrite = < 0.3 mg/day and high nitrite = ≥ 0.3 mg/day from cured meats
				High nitrite/vit +	219	1.3 (1.0–1.7)		
				P for trend		0.002		
				Low nitrite/vit –	46	1.5 (0.93–2.3)		
				High nitrite/vit –	47	2.2 (1.4–3.6)		
				P for trend		0.007		

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Preston-Martin *et al.* (1996); Pogoda & Preston-Martin (2001a,b) (contd)				**Nitrite in cured meat only (mg/day)***				Re-analysis of Preston-Martin *et al.* (1986)
				None	102	1.0 (reference)		*Time-specific nitrite estimates from literature review
				0.01–0.49	293	1.1 (0.8–1.5)		
				0.50–0.99	68	1.9 (1.2–2.9)		
				1.00–1.99	28	1.3 (0.8–2.3)		
				2.00–2.99	12	1.8 (0.8–4.1)		
				≥ 3.00	11	3.0 (1.2–7.9)		
				Per mg/day		β = 0.22 (standard error, 0.08)		Interaction with vitamin use or intake not addressed
				P-value		0.008		

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
International								
Mueller *et al*. (2004), regions near Winnipeg, Canada; Paris, France; Valencia, Spain; and Los Angeles, San Francisco and Seattle, USA; and countries not collecting water (Australia, Israel, Italy), also included in full study; 1976–94	Brain, cranial nerves, cranial meninges, primary malignant	1218 cases in full study from cancer incidence registries in each area, aged < 20 years; > 90.2% histologically confirmed; response rate in each country, 71–88%; 2223 controls in full study from electoral roll, telephone directory, census, population register, health service rosters, or random-digit dialling; response rate in each country, 60–87%	Semi-quantitative test strip estimation of tap-water (collected in 1990s in Canada, France, Spain, USA) from the residence at the time of interview; available for 283 cases and 537 controls (28% of all subjects); including 185 cases and 341 controls, representing 86% subjects from the participating countries who still lived in pregnancy home; including 131 cases and 241 controls with no bottled water use in the home during pregnancy; test strip: minimum 10 mg/L nitrate, 1 mg/L nitrite	**Pregnancy home** *Nitrate in water (mg/L)* All None detected 10–< 25 25–< 50 ≥ 50 No bottled water None detected 10–< 25 25–< 50 ≥ 50 Astroglial tumours None detected 10–< 25 25–< 50 ≥ 50 PNET None detected ≥ 10 Other tumours None detected 10–< 25 25–< 50 ≥ 50	 128 31 12 14 NR NR NR NR NR NR NR NR NR NR NR NR	 1.0 (reference) 0.5 (0.3–0.9) 0.5 (0.2–1.1) 1.0 (0.4–2.2) 1.0 (reference) 0.9 (0.5–1.8) 0.7 (0.2–2.1) 1.5 (0.6–3.8) 1.0 (reference) 0.7 (0.3–1.3) 0.5 (0.1–1.5) 1.9 (0.7–5.7) 1.0 (reference) 0.2 (0.1–0.8) 1.0 (reference) 0.4 (0.2–0.99) 0.6 (0.2–1.6) 0.7 (0.2–2.1)	Study centre, age, sex, year of diagnosis	Among control pregnancy homes, nitrate and nitrite were very prevalent considering that most were on public water supplies at the time of conception: 39.6% any nitrate; 8.2% nitrate ≥ 50 mg/L; 10.0% any nitrite; 2.4% nitrite ≥ 5 mg/L. Results for pregnancy home only presented because these subjects were targeted (others who provided water samples may not be representative; among controls, participation of those not targeted varied according to the presence of nitrite).

Table 2.4. (contd)

Reference, study location, period	Tumour type	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Mueller *et al*. (2004) (contd)				**Nitrite in water (mg/L)**				Results for nitrate not alterered materially when individuals with nitrite detected excluded (nitrite interferes with nitrate measurement using these test strips)
				None detected	160	1.0 (reference)		
				1–< 5	19	1.7 (0.8–3.7)		
				≥ 5	6	2.1 (0.6–7.4)		
				No bottled water				
				None detected	NR	1.0 (reference)		
				1–< 5	NR	2.1 (0.8–6.0)		
				≥ 5	NR	5.2 (1.2–23.3)		
				Astroglial tumours			Center, age, sex, year of diagnosis	
				None detected	NR	1.0		
				1–< 5	NR	4.3 (1.4–12.6)		
				≥ 5	NR	5.7 (1.2–27.2)		
				PNET				
				None detected	NR	1.0		
				1–< 5	NR	0.9 (0.1–11.7)		
				≥ 5	NR	1.3 (0.1–30.9)		
				Other tumours				
				None detected	NR	1.0		
				1–< 5	NR	1.2 (0.3–4.2)		
				≥ 5	NR	0.7 (0.1–7.7)		

CI, confidence interval; NR, not reported; NS, not significant; PNET, primitive neuroectodermal tumours; Q, quartile; T, tertile; vit C, vitamin C; vit-, without vitamin supplement; vit+, with vitamin supplement

by the child (astrocytoma and astrocytic glioma: Preston-Martin *et al*., 1982; Kuijten *et al*., 1990; Bunin *et al*., 1994; primitive neuroectodermal tumours: Bunin *et al*., 1993; brain tumours: McCredie *et al*., 1994a,b; Sarasua & Savitz, 1994; Preston-Martin *et al*., 1996; Schymura *et al*., 1996; Pogoda & Preston-Martin, 2001a,b) but a few other studies did not confirm this (Howe *et al*., 1989; Cordier *et al*., 1994; Lubin *et al*., 2000; medulloblastoma: Bunin *et al*., 2005). Studies in adults have yielded mixed results. Some suggested an increased risk for brain tumours (meningiomas in women: Preston-Martin *et al*., 1982; astrocytoma versus population-based controls: Ahlbom *et al*., 1986; cohort study of glioma: Mills *et al*., 1989; meningioma in men: Preston-Martin *et al*., 1989; Preston-Martin & Mack, 1991; glioma and meningioma: Boeing *et al*., 1993; glioma: Giles *et al*., 1994; gliomas in women: Blowers *et al*., 1997; glioma: Lee *et al*., 1997; Schwartzbaum *et al*., 1999) whereas others did not (meningiomas in men: Preston-Martin *et al*., 1983; astrocytoma versus clinical controls: Ahlbom *et al*., 1986; hospital controls: Burch *et al*., 1987; cohort study of meningioma: Mills *et al*., 1989; glioma in men: Preston-Martin *et al*., 1989; Preston-Martin & Mack, 1991; glioblastoma: Hochberg *et al*., 1990; brain tumours: Kaplan *et al*., 1997; glioma: Chen *et al*., 2002). Meta-analyses of some of the studies cited above suggested an association between consumption of cured meat and the occurrence of brain tumours in children (Huncharek & Kupelnick, 2004) and adults (Huncharek *et al*., 2003), but Murphy *et al*. (1998) observed that trends in the incidence of brain tumour and consumption of cured meat in the two age groups do not support such an association [all three analyses, especially the latter, had limitations that limit inference]. Some studies observed a possible interaction between consumption of cured meat and intake of vitamins (e.g. vitamin C), fruit or vegetables (i.e. the greatest risk is for those who have high consumption of cured meat and a low intake of antioxidants) (Bunin, 1994; Preston-Martin *et al*., 1996; Blowers *et al*., 1997).

2.3.1 *Nitrate*

(a) Ecological studies

Barrett *et al*. (1998) conducted a study (described in detail in Section 2.2) in the Yorkshire region of England, where only 31 (0.3%) of all water samples in public supplies contained > 50 mg nitrate/L. The residence at diagnosis of 3441 (of 3812) cases of brain cancer was linked to a water supply zone ($n = 148$) and its corresponding measurements of nitrate. Relative to the quartile of the population that had the lowest mean concentration of nitrate in water, individuals in all other quartiles (higher levels of nitrate) had a very modest but statistically significant increase in risk for brain cancer (relative risk, 1.14; 95% CI, 1.04–1.26 for the second quartile; 1.13; 95% CI, 1.03–1.25 for the third quartile; and 1.18; 95% CI, 1.08–1.30 for the fourth quartile, adjusted for socioeconomic status and population density).

Van Leeuwen *et al*. (1999) conducted an ecological study (described in detail in Section 2.2) of 40 'ecodistricts' in Ontario, Canada, where levels of nitrate in water ranged from 0 to 91 mg/L nitrate-N. A model that included levels of atrazine as an a-

priori variable and all other potentially confounding factors that were selected according to *p*-value was used to estimate incidence ratios for brain cancer [it was not specified which confounders were retained nor whether any non-significant factors that affected the coefficient for nitrate were appropriately included.] The resulting incidence ratios were non-significantly increased in both men ($P = 0.072$) and women ($P = 0.101$) in relation to increasing levels of nitrate [coefficients not presented].

(b) Case–control studies in adults

Giles *et al*. (1994) conducted a case–control study of primary glioma and diet among adult residents in five major cities in Victoria, Australia, including Melbourne. Cases, aged 20–70 years, were identified at 14 hospitals that had neurological services and were checked against the cancer registry of the region. Controls with no history of stroke, epilepsy or brain tumour were randomly selected from the electoral roll of Victoria that covers 97% of the population. One control was matched to each case by sex and age and subjects with no dietary data were excluded, which resulted in 409 case–control pairs. Odds ratios (tertiles of intake), stratified by gender, were adjusted for alcohol consumption and tobacco smoking. In men, odds ratios for nitrate were modestly and non-significantly above null, while in women, nitrate was associated with a significantly decreased risk for glioma. No dose–response effects were observed in either sex. [Among men, risk estimates for most foods and nutrients, including vitamin C, were above null, which suggests that cases and/or their proxies possibly reported greater food intake in general than controls, although odds ratios were not adjusted for total energy intake. In this particular study, the Working Group believed that this adjustment should have been made because of misclassification, not because energy intake is a potential risk factor.]

Boeing *et al*. (1993) conducted a case–control study of primary incident brain tumours in adult residents of the Rhein–Neckar–Odenwald area of Germany. Cases aged 25–75 years at diagnosis were identified from two neurosurgery clinics that treated 95% of brain tumour patients in the region (115 gliomas, 80 meningiomas, 30 acoustic neuromas); 418 controls were identified by the residential register for the region and were frequency-matched by sex and age. Results were presented for glioma only; odds ratios for dietary intake of nitrate in tertiles were close to null after adjusting for age, sex, alcohol consumption and tobacco smoking. [Steindorf *et al*. (1994) indicated that all controls but only 76.6% of cases had lived in the study region for at least 1 year since 1970 (in the approximately 17 years preceding diagnosis).]

In the same study, Boeing *et al*. (1993) used semiquantitative nitrate test strips (10, 25, 50, 100, 250 and 500 mg/L nitrate) to estimate the levels of nitrate in drinking-water samples from the current residence for a subset of subjects: cases who sent a water sample to the hospital and controls for whom the interviewer conducted the testing during the in-home interview. Proportionally fewer cases than controls provided a water sample (an estimated 60% of cases and 90% of controls, based on Steindorf *et al*. (1994)). [The water-related results are difficult to interpret because only 76.6% of cases but all controls (Steindorf *et al*., 1994) had lived in the study region for at least 1 year since 1970 (in the

approximately 17 years preceding diagnosis); markedly fewer cases than controls provided water samples; a delay in water testing that applied only to cases raises the possibility that the estimates for cases may be systematically biased in relation to those of controls. It is unkown whether the 'current' residence was the residence at diagnosis.]

Steindorf *et al*. (1994), using data from the study by Boeing *et al*. (1993), focused on the 173 cases and 418 controls who had lived in the study region for at least 1 year since 1970. Historical information on residence was linked to data from water-quality monitoring that gave mean nitrate concentrations for each year in 1971–87 obtained from 69 public authorities and water-treatment plants to create indicators of exposure to nitrate in water for 168 (97.1%) cases and 406 (97.1%) controls. (Only 2% of subjects used private wells/springs and supplementary data were attempted for these individuals.) Nitrate values ranged from 0 to 97.8 mg/L and were very similar for cases (15.98 mg/L; standard deviation [SD], 15.61) and controls (16.16 mg/L; SD, 15.72), even when stratified by year of exposure. Odds ratios for estimated exposure to nitrate in quartiles yielded risk estimates for brain tumours at or very close to null, adjusted for age and sex (diet, use of bottled water and tobacco smoking were also considered). The authors indicated that the results were unchanged in subanalyses that considered latency and tumour type. The results of nitrate test strips obtained in Boeing *et al*. (1993) were presented for the subset of subjects (residents of the region) only; nitrate was associated with a decreased risk for brain tumours. [For the test strip results, most of the limitations noted for Boeing *et al*. (1993) apply. These do not apply to the results of water record linkage which suggested that these estimates are valid; when stratified by case status, there was good correlation ($r = 0.62$ in cases and $r = 0.59$ in controls) between the results of water record linkage and another non-gold-standard measure, the test strips. Although this also suggests that the test strips categorized subjects accurately according to nitrate levels within their respective case group (good precision), these results did not provide any information about possible non-differential or differential bias of the test strip measures.]

Kaplan *et al*. (1997) conducted a case–control study of primary adult brain tumours in central Israel. One hundred and thirty-nine cases, aged 18–75 years, were identified from one medical centre that served the region. Two controls (one friend and one orthopaedic patient from the region) of the same sex, age (within 5 years) and ethnic origin were located for each case. Analyses used nutrient densities (nutrient divided by total daily calories) or adjusted for total energy consumption, and were repeated by tumour type (glioma or meningioma) using only one control group at a time. The authors stated that total dietary intake of nitrate was not associated with the occurrence of brain tumours [the number of exposed cases and controls and the risk estimates were not provided].

Blowers *et al*. (1997) conducted a case–control study of gliomas in women and examined their diet. Cases, aged 25–74 years, were identified from a population-based tumour registry in Los Angeles County, CA, USA, and were restricted to 94 glioma patients who were alive and sufficiently well to undergo an interview. For each case, one female control who lived in the same neighbourhood as the case at the time of diagnosis

was selected and matched by age and race (black/white). There was no association between case status and dietary intake of nitrate in quartiles, adjusted for total food intake and body mass index (several other potential confounding factors were also considered). [Exclusion of deceased and very ill cases of glioma somewhat limits the interpretation of the results because surviving cases may not represent incident cases; therefore, selection bias may be possible and results cannot be generalized (such as for stage of tumour or treatment).]

Lee *et al*. (1997) conducted a case–control study of glioma in adults in the San Francisco Bay Area of California, USA. Four hundred and thirty-four cases were identified from a rapid case-ascertainment system at one cancer centre; 439 controls were selected using random-digit dialling and were frequency-matched by age, sex and race/ethnicity (white, black, Hispanic, Asian, other). All comparisons were stratified by sex and adjusted for age, education and family income. Mean weekly intake of nitrate was lower for cases than for controls in both men (non-significant) and women (significant). There was a statistically significant increased risk for glioma in men with high nitrate intake and low vitamin C intake (odds ratio, 2.1; 95% CI, 1.1–3.8; 71 exposed cases).

Chen *et al*. (2002) conducted a case–control study of diet and glioma in adults in eastern Nebraska, USA. Two hundred and fifty-one cases, aged ≥ 21 years, were identified through a cancer registry and 11 hospitals. Controls were mainly selected from among controls of a case–control study of non-Hodgkin lymphoma (that used random-digit dialling and Medicaid records in the same population) and were supplemented by others who were identified by random-digit dialling and death certificates; a total of 498 controls were included and were frequency-matched to cases by age, sex and vital status. Dietary nitrate calculated as nutrient intake in residual quartiles was adjusted for age, sex, respondent type, education, family history of central nervous system tumour and farming and was not significantly associated with the occurrence of glioma.

Ward *et al*. (2005) extended the study by Chen *et al*. (2002) of adult glioma and dietary nitrate by expanding intake of nitrate to drinking-water. This was largely assessed by linking residential histories to data from water quality monitoring for 236 public water sources from 1947 to 1984 (although most analyses presented included only records after 1964, when monitoring became more frequent); the study was restricted to the 130 (52%) cases and 319 (64%) controls who had > 70% person–years of use of public water after 1964 (and up to 1984, which resulted in a 3–8-year lag period before diagnosis). Mean levels assessed by this method ranged from 0 to 12 mg/L nitrate-N. Odds ratios for each quartile above the first quartile were slightly above null, but were non-significant and showed no dose–response pattern. Relative to low levels of nitrate in water and high vitamin C intake, all strata of exposure were above null but were non-significant. The number of years of use of a public water system that contained ≥ 10 mg/L nitrate-N was not associated with risk for glioma nor when 5 mg/L nitrate-N was used as the cut-off point, although the second to first quartile was non-significantly increased. In addition to these analyses, at the time of the interview, 75% of the cases and 60% of 72 controls who had used a private well in 1985 (47 cases, 43 controls) provided a tap-water sample that

was analysed for nitrate. Levels of nitrate ranged from < 0.5 to 67 mg/L nitrate-N. There was no association between this measure (< 10 mg/L nitrate-N versus ≥ 10 mg/L nitrate-N) and case status. The majority of participants relied largely on public water supplies, and only about 15% of cases and controls were believed to have been exposed to 10 mg/L nitrate-N from public water sources for more than 8 years.

(c) Case–control studies in children

Cordier *et al*. (1994) conducted a case–control study of brain tumours in children < 15 years of age in the Paris/Ile de France region of France. Seventy-five cases were identified from 13 hospitals and 113 controls were selected from children who lived in the region through the census agency and telephone books. Relative to the first quartile of nitrate intake during pregnancy, the risk for brain tumours in the offspring in the higher quartiles (adjusted for sex, the age of both the mother and child and maternal education in years) ranged from 0.5 to 1.5, with no dose–response pattern. [Cases and controls differed in several demographic characteristics, including the length of time that mothers had to recall diet during pregnancy, but adjustment was made for several factors as noted above. Unexpectedly, a greater proportion of cases were female than male, but case ascertainment appeared to be complete.]

Lubin *et al*. (2000) conducted a case–control study of children (aged 0–18 years) with brain tumours in relation to diet of both the children and the mothers (during the index pregnancy) in Israel. Three hundred cases, drawn from the Jewish population only, were identified from all neurosurgical departments in Israel and 574 controls were selected from the population registry and were individually matched to cases by sex, birth year and either hospital of birth (in Israel) or country of birth (outside Israel). Based on tertiles of intake, there was no association between the occurrence of brain tumours and intake of nitrate; odds ratios for the upper tertiles were close to null and non-significant relative to the first tertile of intake for both the mother during pregnancy and for the child. [It was not specified whether controls were also required to be Jewish, although intake of nitrate, such as that from pork products, may differ between Jewish and non-Jewish individuals. However, cases and controls were very similar with regard to the ethnic background of the mother as categorized as Asian/African, European/American and Israeli.]

A case–control study of selected types of brain tumour, specifically primitive neuroectodermal tumours (Bunin *et al*., 1993) and astrocytic gliomas (Bunin *et al*., 1994), in children aged < 6 years was conducted on cases identified from 33 paediatric oncology groups in the USA and Canada. One control per case (166 controls matched to primitive neuroectodermal tumours, 155 controls matched to astrocytic gliomas) was identified by random-digit dialling and matched to the case on telephone area code plus the first five digits, date of birth (within 1 year) and race (black/non-black). Increased intake of nitrate was associated in a dose–response fashion with a statistically significantly (P for trend = 0.002) reduced risk for primitive neuroectodermal tumours in the offspring (Table 2.4). However, the inverse association between primitive neuroectodermal tumours and nitrate was attenuated and became non-significant (P for trend = 0.19) after

adjustment for other food components (vitamins A, C and E, folate, nitrite and nitrosamines) and vitamin/mineral supplements. More than 20 other factors relating to the child, the mother and the child's diet were considered, including family income, duration of nausea during pregnancy that interfered with normal eating, duration of breast-feeding and maternal smoking; of these, it appeared that the child's diet of cured meat further attenuated the association reported (fourth versus first quartile of nitrate intake during pregnancy attenuated to 0.81). Dietary nitrate was not associated with risk for astrocyctic glioma in the offspring, and all odds ratios were at or below null after adjustment for family income (and consideration of other factors such as maternal smoking).

Mueller *et al*. (2004) conducted a case–control study of childhood brain tumours and intake of nitrate from drinking-water based on data from four countries: the USA (Mueller *et al*., 2001), Canada, France and Spain. These data were collected as part of a larger international case–control study that also included subjects from Australia, Israel and Italy, but water samples were not collected in these countries. In-person interviews were conducted with the biological mother and, if she was still residing where she had lived during the index pregnancy, a water sample was sought (and obtained from 86% of these women; 185 cases and 341 controls), although water samples were provided by 283 cases and 537 controls. [The Working Group believed that the risk estimates for residences during pregnancy were more valid in terms of exposure assessment because the estimates for post-pregnancy residences may be misclassified due to mothers potentially having changed residence after pregnancy.] Interviewers estimated nitrate using a semiquantitative Merckoquant test strip (10, 25, 50, 100, 250 or 500 mg/L). With adjustment for study region, age, sex and year of diagnosis, there was no increased risk for childhood brain tumours associated with nitrate in tap-water at the residence of pregnancy; however, there was a non-significantly increased risk associated with the highest category of exposure to nitrate after excluding women who used bottled water during pregnancy (odds ratio, 1.5; 95% CI, 0.6–3.8). [Mothers who drank any bottled water were excluded from subanalyses to test reliance on well-water.]

2.3.2 *Nitrite*

(a) Dietary intake of nitrite

(i) *Case–control studies in adults*

Giles *et al*. (1994) conducted a case–control study (described in detail in Section 2.3.1) of adult glioma that linked data on food intake from interviews to published tables of nitrite content. A modest borderline significant increase in risk for glioma was observed among men in relation to estimated dietary intake of nitrite, adjusted for alcohol consumption and tobacco smoking, but with no dose–response relationship. Corresponding odds ratios were close to null among women. [Interpretation of the possible association in men is limited, as noted in Section 2.3.1.]

Boeing *et al*. (1993) conducted a case–control study (described in detail in Section 2.3.1) of adult brain tumours in Germany. The risk for glioma associated with tertiles of dietary nitrite intake was close to null. Nitrite was rarely detected in drinking-water from the current homes of subjects using semiquantitative nitrite test strips. [However this does not reflect the nitrite burden from water in previous places of residence.] The risk estimate for glioma was close to null, while that for meningioma was markedly but non-significantly increased. [Study limitations are noted in Section 2.3.1.]

Kaplan *et al*. (1997) conducted a case–control study (described in detail in Section 2.3.1) of adult brain tumours in Israel. Consumption of approximately 100 foods in the period 10 years before diagnosis was assessed and linked to published tables. The authors stated that dietary intake of nitrite was not associated with the occurrence of brain tumours. [However, neither the number of exposed cases and controls nor risk estimates were provided.]

Blowers *et al*. (1997) conducted a case–control study (described in detail in Section 2.3.1) of glioma in women in southern California, USA. With regard to total nitrite intake and glioma, there was no pattern of association in the risk estimates (P for trend = 0.55), but glioma risk increased with increasing quartiles of nitrite intake from cured meats (P for trend = 0.07). [Study limitations are noted in Section 2.3.1.]

Lee *et al*. (1997) conducted a case–control study (described in detail in Section 2.3.1) of glioma in northern California, USA. All comparisons were stratified by sex and adjusted for age, education and family income. In both men and women, the mean weekly intake of nitrite of glioma cases was slightly [non-significantly] higher than that of controls. In men, the risk for glioma only increased among those with a nitrite intake above the median and a vitamin C intake below the median. This comparison was not significant [interaction p-value not provided.] [For other comments, see Section 2.3.1.] Also, non-participating controls who were asked about vitamin intake reported a higher vitamin intake than participating controls. [It is unknown whether participating and non-participating controls differed with respect to nitrite intake overall or differentially by category of vitamin C intake.]

Schwartzbaum *et al*. (1999) conducted a hospital-based case–control study of glioma and diet in Ohio, USA, among forty cases who underwent their first (exploratory) brain tumour surgery (all histologically confirmed) and 48 age- and sex-matched hospital controls who underwent orthopaedic or gynaecological surgery. Diet was ascertained through a questionnaire and was converted into nitrite intake from cured meats specifically from software and published tables. Just before surgery, 23 (53.5%) cases and 27 (56%) controls provided serum for which results (levels of three antioxidants) were available; these were used to examine the interaction between nitrite and vitamin C/α-tocopherol/γ-tocopherol. Cases had a higher dietary intake of nitrite from cured meat than controls; however, after adjustment for total energy intake, glioma was not associated with an intake of nitrite greater than the median from any of several specific types of cured meat (all odds ratios at or below null). Interaction odds ratios, adjusted for energy, suggested that the risk for glioma was highest among individuals who had an intake of

nitrite from cured meats above the median and levels of intake of vitamin C or α-tocopherol below the median; interaction *p*-values were not provided. [The exclusion criteria for controls that included several diseases related to diet (listed in Table 2.4) probably resulted in a control group that had a different diet (and prevalence of cigarette smoking) from population controls.]

Chen *et al*. (2002) conducted a case–control study (described in detail in Section 2.3.1) of adult glioma in relation to diet in Nebraska, USA. A questionnaire (48 foods) and published literature were used to assess total nitrite intake from the diet, which was not associated with the risk for glioma; there was no interaction between intake of nitrite and that of vitamin C.

Ward *et al*. (2005) (study described in detail in Section 2.3.1) extended the study by Chen *et al*. (2002) to consider the source of the dietary nitrite (animal versus plant) and to estimate the intake of endogenously formed nitrite from drinking-water (5% of the estimated nitrate intake from drinking-water). For most subjects, nitrate intake from water was estimated by linking histories of residence to data from public water-quality monitoring (mainly for 1965–85 for 130 (52%) cases and 319 (64%) controls). For a small subset of subjects who used private wells in 1985 and who provided a water sample, nitrite was estimated by laboratory analysis. As in the larger study, odds ratios for quartiles of total dietary intake of nitrite were close to null, and there was no interaction with intake of vitamin C (Chen *et al*., 2002). Odds ratios for nitrite from animal sources were also close to null and not statistically significant, but those for the upper two quartiles of nitrite from plant sources were markedly increased and statistically significant. When total nitrite intake from all dietary sources was combined with the estimated intake of nitrite from drinking-water, odds ratios were again close to null, with the exception of the second (versus the first) quartile (odds ratio, 1.8; 95% CI, 0.9–3.6). There was no interaction between this combined (diet and water) nitrite variable and vitamin C, nor between nitrite from water and either vitamin C or smoking status. [See comments in Section 2.3.1.]

(ii) *Case–control studies in children*

Cordier *et al*. (1994) conducted a case–control study (described in detail in Section 2.3.1) of childhood brain tumours in France. Maternal intake of selected foods during pregnancy was ascertained by structured interview and linked to a national survey and published tables to estimate total intake of nitrite. Odds ratios for brain tumours in the offspring were estimated by quartiles of nitrite intake, and a non-significant inverse dose–response relationship was observed [for possible limitations, see Section 2.3.1].

Lubin *et al*. (2000) conducted a case–control study (described in detail in Section 2.3.1) of childhood brain tumours and consumption of nitrite in childhood and during the index pregnancy in Israel. There was no association between brain tumours and intake of nitrite; odds ratios for the upper tertiles were close to null relative to the first tertile for intake by both the mother during pregnancy and the child. [See Section 2.3.1 for possible study limitations.]

Bunin *et al*. (1993, 1994) conducted a case–control study (described in detail in Section 2.3.1) of primitive neuroectodermal tumours and astrocytic gliomas in children < 6 years of age and their possible association with maternal dietary levels of nitrite in Canada and the USA. Intake of nitrite during pregnancy was not associated with the risk for either primitive neuroectodermal tumours or astrocytic gliomas in the offspring. Risk estimates for the latter were adjusted by family income, and numerous other potentially confounding factors were also considered (see Section 2.3.1).

Preston-Martin *et al*. (1996) conducted a case–control study of childhood brain tumours and diet in the states of California and Washington, USA. Five hundred and forty cases were identified from three tumour registries, and 801 controls, who were identified by random-digit dialling, were frequency-matched to cases by age and sex. A questionnaire (47 foods) was administered to biological mothers to identify the frequency and amounts of intake during the index pregnancy; these data were subsequently linked to published food tables and other software to determine levels of intake of nitrite. Odds ratios were adjusted for age, sex, birth year and geographical area; race and socioeconomic status were also considered but had no confounding effect. Risk for childhood brain tumour was not associated with total dietary nitrite or total intake of nitrite from vegetables. The highest quartile of nitrite intake from cured meats, however, was associated with a significantly increased risk for childhood brain tumours (odds ratio, 1.9; 95% CI, 1.3–2.6; 155 exposed cases), and yielded a significant *p* value for trend ($P = 0.003$); risk estimates for the second and third quartiles were close to null. The *p* value for trend was also significant among subjects with low and high socioeconomic status. When the authors considered the interaction between nitrite from cured meat and the use of prenatal vitamin supplements, no significant effect was observed, but the risk for brain tumours was increased in those with a high (above median) intake of nitrite from cured meats and no prenatal use of vitamins relative to those with an intake below the median plus prenatal use of vitamins (odds ratio, 2.2; 95% CI, 1.4–3.6; 47 exposed cases).

Pogoda and Preston-Martin (2001a) extended this work to refine the levels of nitrite linked to the earlier (Preston-Martin *et al*., 1996) data on diet using 26 food surveys with data on sodium nitrite to consider levels of nitrite in specific cured meats according to the year of consumption (index pregnancy). This updated study also allowed greater flexibility in the modelling (splines), with adjustment for the same confounding factors as before. Results were consistent with the previous study, and were more pronounced. The authors also estimated the increase in risk associated with 1 mg per day increase in nitrite consumption (from cured meat) during pregnancy, which was statistically significant ($P = 0.008$).

(b) Intake of nitrite from water

Mueller *et al*. (2004) conducted a case–control study (described in detail in Section 2.3.1) of childhood brain tumours and nitrite from drinking-water in Canada, France, Spain and the USA. Interviewers used semiquantitative Merckoquant test strips to estimate nitrite levels in tap-water samples from the current residence, which were sought

if this was the same residence as that of the index pregnancy. A sample was obtained from 86% of these women (185 cases and 341 controls), although water samples were provided by 283 cases and 537 controls. Among the latter, there was no increased risk for brain tumours in children in relation to the presence of nitrite in tap-water. [Subjects who no longer lived at the same residence as that at the time of pregnancy but who provided water samples may not be representative; among controls, participation of those who no longer lived at the pregnancy home varied according to the presence of nitrite.] When water samples were collected from homes in which the index pregnancy occurred, increasing levels of nitrite in water were associated with an increased risk for brain tumours in the offspring. This association was stronger (and statistically significant for the highest level of nitrite) when analyses were further restricted to women who did not drink any bottled water in the home during pregnancy. The increased risk was present only with respect to astroglial tumours; risk estimates for both primitive neuroectodermal tumours and other tumour types were close to null. [Among the pregnancy homes of controls, most of whom used public water supplies at the time of conception, nitrate and nitrite were very prevalent: 39.6% any nitrate, 8.2% nitrate ≥ 50 mg/L, 10.0% any nitrite and 2.4% nitrite ≥ 5 mg/L. Because levels of nitrite were usually low in public water supplies, it is unknown whether this reflects measurement error and, if so, whether it could differ by case status; however, it is unlikely to differ by histological tumour type, although the association was confined to astroglial tumours. Also, it should be noted that the levels of nitrite in tap-water may correlate with other substances in the water, such as pesticides and trichloromethanes.]

2.4 Cancer of the urinary tract

2.4.1 *Ingested nitrate*

(a) Ecological studies (Table 2.5)

Ecological studies in Europe have evaluated concentrations of nitrate in the drinking-water in relation to mortality from or incidence rates of cancer of the urinary tract (urinary bladder, lower urinary tract (comprised largely of bladder cancers) and kidney). Generally, these studies obtained concentrations of nitrate in water for a specific time period from public water supply databases and computed rate ratios, mortality rates or standardized incidence ratios (SIR) or compared incidence rates for regions grouped according to their average concentrations of nitrate.

In northern Jutland, Denmark, Jensen (1982) computed incidence rates (age standardized to the European standard population) of cancers of the urinary tract for Aalborg, a town that had high levels of nitrate in the water, and Aarhus, a town that had low levels. Levels of nitrate in municipal water averaged 27.1 mg/L in Aalborg in 1976 and had been detected since the 1930s, i.e. for at least 50 years; average levels in Aarhus were 0.2 mg/L in 1976 (described in detail in Section 2.2). No significant differences in incidence rates (per 100 000 persons) were observed between the two towns.

Table 2.5. Ecological studies of ingested nitrate and tumours of the urinary tract and genital tumours

Reference, location	Organ site (ICD code)	End-point	Exposure assessment	Exposure categories	No. of cases/ deaths	Main results		Adjustment for potential confounders	Comments
Jensen (1982), northern Jutland, Denmark	Urinary system, male genital organs, uterus, other female genital organs, breast	Incidence of urinary system cancers, 1968–72	Annual average concentrations of nitrate for the municipality of Aalborg (27.1 mg/L) and Aarhus (0.2 mg/L) in 1976	Mean nitrate (mg/L)		Incidence rate per 100 000		Rates age-standardized to the European standard population	
						Men	**Women**		
						Urinary tract			
				Aalborg		43.7	15.1		
				Aarhus		47.3	19.1		
						Male genital organs			
				Aalborg		49.9			
				Aarhus		47.8			
						Uterus			
				Aalborg			70.5		
				Aarhus			49.0		
						Other female genital organs			
				Aalborg			27.5		
				Aarhus			24.7		
						Breast			
				Aalborg		1.2	75.8		
				Aarhus		0.4	76.5		
Morales-Suárez-Varela *et al*. (1993, 1995), Valencia, Spain; 261 (1993) and 258 (1995) municipalities	Bladder (188), prostate (185)	Mortality, 1975–88	Concentrations of nitrate in public drinking-water, 1975–80 (1993) and 1968 (1995)	Mean nitrate (>50 mg/L) versus all other concentrations for municipalities		**Rate ratio (95% CI)** *Bladder* Men, 1.31 (0.64–2.71) Women, 2.1 (0.42–10.39) All, 1.38 (0.68–2.8)		Rate ratio based on mortality rates directly age-standardized to the 1981 Spanish population	Number of deaths not provided

Table 2.5 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure assessment	Exposure categories	No. of cases/ deaths	Main results	Adjustment for potential confounders	Comments
Morales-Suárez-Varela *et al*. (1993, 1995) (contd)				**Concentrations of nitrate in municipality (mg/L)**		**Mortality rates [per 100 000 persons/year]**	Age-adjusted mortality rates (direct method)	
					Men	*Bladder*		
				0–25	569	9.9		
				25–50	25	7.32		
				> 50	14	8.41		
					Women			
				0–25	112	2.03		
				25–50	0	–		
				> 50	0	–		
					Men	*Prostate*		
				0–25	925	16.9		
				25–50	58	16.9		
				> 50	40	24.04		
Van Leeuwen *et al*. (1999), Ontario, Canada	Bladder	Incidence of bladder cancer, Ontario Cancer Registry, 1987–91	Nitrate in drinking-water, 1987–91; 40 'ecodistricts' of Ontario	Mean concentrations of nitrate in the ecodistrict		No correlation was observed in women or men	Age-standardized	

Table 2.5 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure assessment	Exposure categories	No. of cases/ deaths	Main results	Adjustment for potential confounders	Comments
Gulis *et al.* (2002), Trnavas District, Slovakia	Bladder (188), kidney (189)	Cancer incidence from regional cancer registry, 1986–95	Concentrations of nitrate in 60 municipal supplies, 1975–95	**Average level of nitrate (mg/L)**		SIR (95% CI)	SIR based on age- (10-year), calendar year- and sex-specific incidence rates for the district	
						Bladder		
						Men		
				0–10	30	1.18 (0.82–1.68)		
				10.1–20	53	1.09 (0.83–1.43)		
				> 20	43	0.97 (0.71–1.30)		
						P for trend = 0.25		
						Women		
				0–10	13	1.32 (0.76–2.28)		
				10.1–20	15	0.81 (0.49–1.34)		
				> 20	14	0.82 (0.48–1.38)		
						P for trend = 0.13		
						Kidney		
						Men		
				0–10	14	0.99 (0.58–1.67)		
				10.1–20	29	1.06 (0.74–1.53)		
				> 20	26	1.11 (0.75–1.62)		
						P for trend = 0.53		
						Women		
				0–10	4	0.50 (0.19–1.32)		
				10.1–20	16	1.07 (0.66–1.75)		
				> 20	13	0.96 (0.55–1.64)		
						P for trend = 0.15		

Table 2.5 (contd)

Reference, location	Organ site (ICD code)	End-point	Exposure assessment	Exposure categories	No. of cases/ deaths	Main results		Adjustment for potential confounders	Comments
Volkmer *et al*. (2005), Bocholt, Germany	Urinary tract, testis, penis, prostate	Incidence of genitourinary tract cancers derived from medical facilities and practices, 1985–97	Concentrations of nitrate from two waterworks, 1957–85	Nitrate (60 mg/L versus 10 mg/L)	527 total	**SIR (95% CI)**		Age standardi-zation based on the German population in 1993	
						Transitional-cell carcinoma of the urinary tract			
					NR	Men	2.26 (1.34–3.79)		
					NR	Women	1.52 (0.78–2.96)		
					210	Total	1.98 (1.10–3.54)		
						Renal-cell carcinoma			
					NR	Men	0.61 (0.28–1.33)		
					NR	Women	2.96 (0.66–13.18)		
					57	Total	0.87 (0.34–2.22)		
					42	Testis	0.43 (0.21–0.90)		
					9	Penis	0.66 (0.14–2.88)		
					209	Prostate	1.06 (0.76–1.48)		

CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; SIR, standardized incidence ratio

Morales-Suarez-Varela *et al*. (1993) studied cancer of the urinary bladder in Valencia, Spain, a region that has the highest reported levels of nitrate in the drinking-water in Europe. Mean concentrations of nitrate for 261 municipalities in the region were derived for the period 1975–80 from data obtained from the Department of Public Health, Hygiene and Environment. Mortality rates for urinary bladder cancer (International Classification of Diseases (ICD)-9 188) for the period 1975–88 were calculated from national death records and standardized directly for age and sex to the 1981 Spanish population. Compared to other regions, mortality rates in municipalities where water contained levels of > 50 mg/L nitrate were 38% higher overall, 31% higher among men and twice as high among women; however, these excesses were not statistically significant. [The Working Group noted that this study does not report the actual number of deaths from bladder cancer and the confidence intervals indicate imprecise rate ratios.] A subsequent report from Morales-Suárez-Varela *et al*. (1995) examined mortality rates for cancer of the urinary bladder (described in detail in Section 2.2). As in the previous study, deaths from cancer were obtained from national records (ICD-9 188 for bladder cancer) for 1975–88. Data from 268 municipalities were grouped into three categories of estimated concentrations of nitrate in the drinking-water (0–25, 25–50 and > 50 mg/L). Mortality rates for bladder cancer (directly age-standardized [standard population unspecified]) were similar across exposure categories for men: 9.9, 7.32 and 8.32 [per 100 000 person–years], respectively. In women, the rate was 2.03 [per 100 000 person–years] in the lowest exposure category and could not be computed for the other levels because there were no deaths.

An ecological study in Ontario, Canada (described in detail in Section 2.2) examined the incidence of urinary bladder cancer in relation to average concentrations of nitrate in 40 'ecodistricts' (Van Leeuwen *et al*., 1999). The authors indicated that no correlation was detected among men or women ($P > 0.25$), when levels of atrazine, alcohol consumption, tobacco smoking, level of education, income and occupational exposures derived from a provincial health survey were taken into account. [No correlations or risk estimates were provided.]

A study in the agricultural district of Trnava, Slovakia (Gulis *et al*., 2002), computed incidence rates for urinary bladder cancer in 60 villages that used municipal water systems (described in detail in Section 2.2). Villages were grouped into three categories based on the average concentrations of nitrate in their water supplies for the period 1975–95 (0–10, 10.1–20 and ≥ 20 mg/L nitrate). Using data from the regional cancer registry for the period 1986–95, sex-specific SIRs were computed for cancers of the urinary bladder (ICD-0 188) and kidney (ICD-0 189) with incidence rates for the entire district as the standard, stratified by age (10 years) and calendar year. SIRs did not increase with exposure category for either bladder or kidney cancer (SIRs for bladder cancer, 1.22, 1.18 and 1.32; SIRs for kidney cancer, 0.81, 1.05 and 1.05, respectively).

An ecological analysis was performed in a community of Bocholt, Germany, that was served by two waterworks over a period of 28 years (Volkmer *et al*., 2005). Concentrations of nitrate were distinct for the two waterworks: between 1957 and 1985,

one contained 60 mg/L nitrate and the other 10 mg/L, but both contained 10 mg/L nitrate from 1986 to 1997. Newly diagnosed cancers of the urinary tract among inhabitants of Bocholt were identified from medical departments (urology, pathology, oncology, radio-oncology) and outpatient urology practices between July 1985 and June 1997. Incidence rates in the two exposure groups were standardized to the German population for 1993. Rate ratios were higher in the area with higher levels of nitrate in 1957–85 for transitional carcinomas of the urinary tract (1.98; 95% CI, 1.10–3.54; overall rate ratio in men, 2.26; 95% CI, 1.34–3.79; overall rate ratio in women, 1.52; 95% CI, 0.78–2.96). For renal carcinomas, rate ratios were not increased overall among the high-nitrate group (0.87; 95% CI, 0.34–2.22); however, the rate ratio was above one among women (2.96; 95% CI, 0.66–13.18) and below one among men (0.61; 95% CI, 0.28–1.33), although, neither was statistically significant. [The investigators determined tobacco smoking histories from the medical records of the cases and these were not statistically significantly different between the two exposure groups; 15.9% in the high-exposure group and 20.6% in the low-exposure group had smoked > 20 pack–years; however, smoking could not be adjusted for in the analysis and the possibility of confounding remains. Further, the level of completion of case ascertainment is uncertain.]

(b) Cohort study (Table 2.6)

The US Iowa Women's Health Study (Weyer *et al*., 2001) evaluated nitrate in both the diet and drinking-water in relation to the incidence of cancers of the urinary bladder and kidney. This was a prospective study of 21 977 women who were 55–69 years of age in 1986 (response rate, 43%) and who used the same water supply for more than 10 years (87% used the same water supply for more than 20 years). The baseline postal questionnaire included basic demographic information, cigarette smoking history and a 126-item food-frequency questionnaire (the 1984 version of the Nurses' Health Study) which asked about usual diet in the previous year. A follow-up postal questionnaire in 1989 asked about the type of water system at the current residence and duration of use. Concentrations of nitrate in municipal water systems were analysed by the University of Iowa's Hygienic Laboratory in 1955–64, 1976–82 and 1983–88. Only communities that used a 'single source' (surface source or specific aquifer for 90% of their water) were included; users of private wells formed a separate stratum. Cancers diagnosed through to 31 December 1998 were determined by linkage to the Iowa State Cancer Registry. After adjustment for age and total energy intake, relative risks for kidney cancer were non-significantly elevated in the top three quartiles of dietary intake of nitrate (> 11.6 mg nitrate-N); however, there was no clear evidence of a trend in risk across quartiles. For urinary bladder cancer, relative risks were slightly and non-significantly elevated in the top three quartiles of dietary nitrate intake, but again there was no consistent increase with increasing exposure. Using average levels of nitrate in water (all years), relative risks were

Table 2.6. Cohort study of ingested nitrate and tumours of the urinary tract and genital tumours

Reference, location, name of study	Description of the cohort	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weyer *et al.* (2001), Iowa, USA, Iowa Women's Study	Cohort of 21 977 Iowa women, 55–69 years of age in 1986, who had a valid driver's licence and no previous history of cancer and who had used the same water supply for > 10 years (87% > 20 years), linked to the Iowa Cancer Registry 1986–98; response rate, 43%	Mailed baseline questionnaire in 1986 included tobacco smoking and other factors and a 126-item food-frequency questionnaire (adapted from the 1984 version of the Nurses' Health Study); a follow-up questionnaire in 1989 included type of water system of current residence and duration of use.	Bladder, kidney, breast, ovary, uterine corpus	**Diet nitrate (mg nitrate–N)**			Age, total energy	Investigators did not examine interaction with vitamin C; for use of private wells, odds ratios were 1.31 (95% CI, 0.48–3.55) for bladder cancer and 1.07 (95% CI, 0.45–2.57) for kidney cancer.
						Bladder		
				< 11.6	9	1.00 (reference)		
				11.6–18.0	17	1.88 (0.84–4.24)		
				18.1–27.2	13	1.46 (0.62–3.47)		
				> 27.2	14	1.57 (0.66–3.75)		
						Kidney		
				< 11.6	12	1.00 (reference)		
				11.6–18.0	15	1.32 (0.62–2.83)		
				18.1–27.2	14	1.32 (0.60–2.89)		
				> 27.2	14	1.37 (0.61–3.06)		
						Breast		
				< 11.6	253	1.00 (reference)		
				11.6–18.0	252	0.98 (0.83–1.17)		
				18.1–27.2	265	1.04 (0.87–1.24)		
				> 27.2	254	0.99 (0.83–1.19)		
						Ovary		
				< 11.6	24	1.00 (reference)		
				11.6–18.0	28	1.12 (0.65–1.94)		
				18.1–27.2	28	1.10 (0.63–1.92)		
				> 27.2	22	0.85 (0.47–1.55)		
						Uterine corpus		
				< 11.6	71	1.00 (reference)		
				11.6–18.0	41	0.60 (0.41–0.88)		
				18.1–27.2	51	0.78 (0.54–1.12)		
				> 27.2	61	0.97 (0.68–1.39)		

Table 2.6 (contd)

Reference, location, name of study	Description of the cohort	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weyer *et al.* (2001) (contd)		Nitrate concentrations were derived from municipal water supplies over the periods 1955–64, 1976–82, 1983–88; average nitrate level computed over the 33-year time frame for communities using a 'single source' for 90% of their water and average level for 1955–64 exclusively; users of private wells formed a separate stratum		**Mean nitrate in water (mg/L nitrate–N) 1955–88**			Age, education, tobacco smoking (never/former/current and pack–years), physical activity, body mass index, waist-to-hip ratio, total energy, intakes of vitamin C, vitamin E, and fruits and vegetables (for water nitrate), dietary nitrate, water source (ground/surface)	
						Bladder		
				< 0.36	7	1.00 (reference)		
				0.36–1.00	14	1.69 (0.66–4.30)		
				1.01–2.46	8	1.10 (0.38–3.20)		
				> 2.46	18	2.83 (1.11–7.19)		
						Kidney		
				< 0.36	9	1.00 (reference)		
				0.36–1.00	1	1.34 (0.55–3.25)		
				1.01–2.46	13	1.38 (0.56–3.41)		
				> 2.46	12	1.20 (0.46–3.16)		
						Breast		
				< 0.36	208	1.00 (reference)		
				0.36–1.00	209	1.03 (0.84–1.26)		
				1.01–2.46	185	0.97 (0.78–1.20)		
				> 2.46	208	1.03 (0.83–1.28)		
						Ovary		
				< 0.36	13	1.00 (reference)		
				0.36–1.00	19	1.52 (0.73–3.17)		
				1.01–2.46	24	1.81 (0.88–3.74)		
				> 2.46	26	1.84 (0.88–3.84)		
						Uterine corpus		
				< 0.36	44	1.00 (reference)		
				0.36–1.00	44	0.86 (0.55–1.35)		
				1.01–2.46	48	0.86 (0.55–1.36)		
				> 2.46	32	0.55 (0.33–0.92)		

CI, confidence interval

higher among those in the top quartile (> 2.46 mg/L nitrate-N) versus the lowest quartile (< 0.36 mg/L nitrate-N) for bladder cancer (relative risk, 2.83; 95% CI, 1.11–7.19); for kidney cancer, the relative risk was 1.20 (95% CI, 0.46–3.16) [the mean concentration for the top quartile was 5.59 mg/L nitrate-N]. Use of private wells was more weakly associated with bladder cancer (relative risk, 1.31; 95% CI, 0.48–3.55) and appeared to be unrelated to kidney cancer. Results were similar for an additional analysis that was restricted to 1955–64 and to women who had lived in the same residence for > 20 years. Relative risks for nitrate in water and use of private wells were adjusted for multiple potentially confounding factors such as age, education, tobacco smoking, pack–years of smoking, physical activity, body mass index, waist-to-hip ratio, total energy, vitamin C, vitamin E and fruit and vegetable intake, dietary intake of nitrate and type of water source (ground-versus surface). [Although the study did not ascertain sources of drinking-water outside the home, only 33% of women worked away from home; the study did not account for the amount of water consumed on an individual level. There was no assessment of potential effect modification, i.e. by vitamin C intake.]

(c) Case–control studies (Table 2.7)

One case–control study examined ingested nitrate in relation to cancer of the urinary bladder (Ward *et al*., 2003). Assessment of exposure to nitrate included evaluation of dietary intake and concentrations in the drinking-water. One small study of bladder cancer that analysed urinary concentrations of nitrate after diagnosis was not reviewed because the cancer potentially could have affected the levels of nitrate.

A large population-based case–control study of bladder cancer was conducted in Iowa, USA, and investigated intake of nitrate in both the diet and drinking-water (Ward *et al*., 2003). Cases included 1452 histologically confirmed bladder cancers that were newly diagnosed between 1986 and 1989, who were between the ages of 40 and 85 years and had no history of malignancy (except for basal-cell or squamous-cell carcinoma of the skin). These were identified by the Iowa State Cancer Registry and controls were selected from driver's licence records (for those aged < 65 years) and US Health Care Finance Administration records (for those aged 65 years and older). Reported response rates were 85% for cases and 82% for controls. Subjects were mailed a questionnaire that covered demographic information, history of cigarette smoking, occupation and lifetime residences and sources of drinking-water, together with a 55-item food-frequency questionnaire that asked about usual adult diet. Dietary levels of nitrate were based on the published literature and were analysed in quartiles. There was no evidence of an association between dietary intake of nitrate among men (odds ratio, 0.9; 95% CI, 0.7–1.1 for ≥ 119 versus < 59 mg nitrate per day) or women (odds ratio, 0.8; 95% CI, 0.5–1.3 for ≥ 127 versus < 62 mg nitrate per day). Estimates of exposure to nitrate from drinking-water were based on residential concentrations of nitrate. Questions included the amount of tap-water consumed in and outside the home, but the latter accounted for only 10% of consumption. Samples taken from the distribution system in a given year were averaged and linked to an individual by year and town. When no data were available for that year and

Table 2.7. Case–control studies of ingested nitrate and nitrite and tumours of the urinary tract and genital tumours

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Barbone *et al*. (1993), Birmingham, AL, USA, 1985–88	Endo–metrial	168 women with endometrial cancer, 1985–1988, identified at the University of Alabama Hospital and a large private gynaecology–oncology practice in Birmingham, AL	334 women with an intact uterus attending the University optometry clinic; matched on age, race	Nurses' Health Study FFQ (116-item) administered in person with the assistance of the interviewer 103 cases and 236 controls	**Dietary nitrate (calorie adjusted mg)** T 1 (< 94.0) T 2 (94.0–<150.5) T 3 (≥ 150.5) *P* for trend	 48 29 26	 1.0 (reference) 0.7 (0.4–1.2) 0.4 (0.2–0.8) 0.0057	Age, race, years of schooling, total calories, use of unopposed estrogens, obesity, shape of obesity, smoking, age at menarche, number of pregnancies, diabetes, hypertension	

Table 2.7 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Wilkens *et al*. (1996), Oahu, Hawaii, USA, 1979–86	Lower urinary tract cancer (90% urinary bladder, 7% renal pelvis, 3% ureter)	261 cases (195 men, 66 women) of Caucasian or Japanese ancestry; 1977–86, hospitals covering 95.5% of eligible cases in the Hawaii Tumor Registry	522 population controls (390 men, 132 women); matched on sex, age (± 5 years), ethnic group; identified from Health Surveillance Program (annual survey of 2% of the population)	29-item dietary history of diet in a usual week one year prior to the reference date	**Dietary nitrites (µg/week)** *Men* Japanese T 1 T 2 T 3 *P* for trend Caucasian T 1 T 2 T 3 *P* for trend *Women* Japanese T 1 T 2 T 3 *P* for trend Caucasian T 1 T 2 T 3 *P* for trend	NR	 1.0 (reference) 1.2 (0.6–2.4) 2.0 (1.0–4.0) 0.05 1.0 (reference) 0.9 (0.5–1.6) 0.6 (0.3–1.2) 0.10 1.0 (reference) 0.5 (0.2–1.6) 0.9 (0.3–2.5) 0.84 1.0 (reference) 0.3 (0.1–1.1) 0.9 (0.3–2.4) 0.81	Age, cigarette smoking status, pack/years, employment in a high-risk occupation (both men and women), consumption of dark green vegetables (men), total vitamin C intake (women)	The mean intake of nitrate (µg/week) was reported as 1.95 in male cases, 1.84 in male controls, 1.14 in female cases and 1.32 in female controls [the Working Group questioned that the unit was more probably mg/week]. The odds ratios for nitrosamine in Japanese were 1.9 (95% CI, 0.9–4.3) and 3.0 (95% CI, 1.4–6.4) for tertiles 2 and 3 compared with tertile 1 in men and 1.0 (95% CI, 0.3–3.3) and 1.9 (95% CI, 0.6–5.8), respectively, in women.

Table 2.7 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Møller (1997), Denmark, 1986–88	Testicular cancer	514 men born between 1916 and 1970 identified by the Danish Cancer Registry; response rate, 88%	720 men selected randomly from the Danish population; matched on year of birth; response rate, 69%	Telephone interviews	**Born in high nitrate area**			Year of birth	
					Total	31	1.27 (0.99–1.64)		
					Non-seminoma	30	1.28 (0.91–1.80)		
					Seminoma	32	1.27 (0.93–1.74)		
					Lived in high nitrate area for the larger part of childhood				
					Total	32	1.40 (1.09–1.81)		
					Non-seminoma	33	1.49 (1.06–2.08)		
					Seminoma	33	1.36 (1.00–1.86)		
					High nitrate in childhood in the country				
					Total	18	1.10 (0.79–1.53)		
					Non-seminoma	17	1.04 (0.66–1.62)		
					Seminoma	19	1.14 (0.76–1.72)		
					High nitrate in childhood not in the country				
					Total	15	1.51 (1.03–2.20)		
					Non-seminoma	16	1.74 (1.07–2.82)		
					Seminoma	14	1.37 (0.86–2.20)		

Table 2.7 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2003), Iowa, USA, 1986–89	Urinary bladder	1452 cases (1135 men, 317 women) newly diagnosed and histologically confirmed, aged 40–85 years, identified from the Iowa State Health Registry; response rate, 85%	2434 population-based controls (1601 men, 833 women) from driver's licence records or US Health Care Finance Administration; frequency-matched on age, sex at a different ratio in 1986–87 and 1988–89; response rate, 82%	Mailed questionnaire covering basic demographics smoking, occupation, residential and water source history, well depth and a 55-item FFQ on usual adult diet.	**Dietary nitrate (mg/day)** *Men* > 59 59–< 84 84–< 119 ≥ 119 *Women* < 62 62–< 90 90–< 127 ≥ 127 **Dietary nitrite (mg/day)** *Men* < 0.81 0.81–< 1.06 1.06–< 1.39 ≥ 1.39 *Women* < 0.58 0.58–< 0.75 0.75–> 0.98 > 0.98	NR	 1.0 (reference) 0.8 (0.7–1.1) 0.9 (0.7–1.2) 0.9 (0.7–1.1) 1.0 (reference) 1.2 (0.8–1.9) 0.9 (0.5–1.4) 0.8 (0.5–1.3) 1.0 (reference) 1.1 (0.9–1.4) 1.2 (0.9–1.5) 1.2 (0.9–1.6) 1.0 (reference) 1.0 (0.6–1.5) 0.8 (0.5–1.3) 1.0 (0.7–1.6)	Age, cigarette smoking, education, duration of chlorinated surface-water use, study period	Water analysis restricted to those who used Iowa public water systems with known nitrate level for ≥ 70% of their person–years starting in 1960. No evidence of a positive trend by years of use of a public water supply ≥ 10 mg/L nitrate-N. No positive association between use of private wells and risk.

Table 2.7 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (2003) (contd)				Residential concentrations of nitrate in water 1960 onwards; average concentrations and number of years of public water supply with ≥ 10 mg/L examined	**Nitrate in water (mg/L nitrate-N)**				
					Men				
					< 0.6	171	1.0 (reference)		
					0.6–< 1.40	171	0.9 (0.6–1.2)		
					1.40–< 3.09	164	0.8 (0.6–1.1)		
					≥ 3.09	116	0.5 (0.4–0.8)		
					Women				
					< 0.67	57	1.0 (reference)		
					0.67–< 1.18	44	0.7 (0.4–1.2)		
					1.18–< 2.48	38	0.6 (0.3–1.1)		
					≥ 2.48	47	0.8 (0.4–1.3)		
					High vitamin C	*(≥130 mg/day)*		Age, gender, smoking, duration, chlorinated surface water, education, study period	Nitrate (mg/L nitrate-N): low (< 1.25) high (≥ 1.25)
					Low nitrate	169	1.0 (reference)		
					High nitrate	134	0.7 (0.5–1.0)		
					Low vitamin C	*(<130 mg/day)*			
					Low nitrate	171	0.8 (0.6–1.1)		
					High nitrate	158	0.7 (0.5–0.9)		

CI, confidence interval; FFQ, food-frequency questionnaire; T, tertile

the sources did not vary more than 10%, a weighted average of annual averages in adjacent years was used (with greater weights closer to the year without data); missing values were assigned when no data were available within 10 years. The analyses were restricted to persons who used Iowa public water systems with known levels of nitrate for 70% or more of their person–years starting in 1960, and individual levels of nitrate were assigned based on the average levels after 1960. The risk for bladder cancer was unrelated to quartiles of nitrate-N (mg/L) among women and, if anything, lower among men. This risk was statistically significant for the highest exposure quartile (odds ratio, 0.5; 95% CI, 0.4–0.8 for ≥ 3.09 versus < 0.6 mg/L nitrate-N) and similar after accounting for number of years of use of water that contained levels of ≥ 10 mg/L nitrate-N after 1934. Estimates were adjusted for age, education, cigarette smoking, years of use of chlorinated surface water and study period. Further, there were no apparent interactions between exposure to nitrate from water and vitamin C intake, ever having had a bladder or kidney infection or smoking status. The authors also stated that duration of use of private wells and duration of use of wells less than 50 feet [15.2 m] deep were weakly inversely related to the risk for bladder cancer among men and unrelated to the risk among women [the point estimates were not provided].

2.4.2 *Ingested nitrite*

Two case–control studies of dietary intake of nitrite and cancer of the urinary bladder or lower urinary tract have been conducted, but no cohort studies. Case–control studies that used urinary concentrations of nitrite after diagnosis were excluded (for reasons provided in Section 2.4.1). The reviewed case–control studies of nitrite and urinary tract tumours are summarized in Table 2.7.

A population-based case–control study (Wilkens *et al*., 1996) from Oahu, Hawaii, USA, evaluated dietary intake of nitrites in relation to cancers of the lower urinary tract. The study included 195 men and 66 women of Caucasian or Japanese ancestry who were newly diagnosed with a lower urinary tract cancer between 1977 and 1986 at the seven largest civilian hospitals on the Island of Oahu (covering an estimated 95.5% of eligible cases based on the state cancer registry). Response rates were 89% for controls and 73% for living cases. Ninety per cent of the cases had tumours of the urinary bladder, 7% of the cancer of renal pelvis and 3% cancer of the ureter. Controls were selected from the Health Surveillance Program of the Hawaii State Department of Health (a survey of a 2% random sample of the population with participation rates of over 95%) and comprised 390 men and 132 women who had no history of a lower urinary tract tumour and who were matched to each case on sex, age (± 5 years) and ethnic group. A dietary history was obtained by personal interview that included a 29-item questionnaire that was designed to determine foods that contain nitrite and nitrosamines consumed in a usual week in the year before the reference date. Estimates of nitrite intake were obtained from published US Department of Agriculture tables. Among men of Japanese ancestry, there was a twofold risk for urinary tract cancers in the highest tertile of nitrite intake versus the

lowest tertile (odds ratio, 2.0; 95% CI, 1.0–4.0; *P* for trend = 0.05). The inverse was observed among Caucasian men (highest versus lowest tertile odds ratio, 0.6; 95% CI, 0.3–1.2), but not women. A statistically significant trend in risk (*P* = 0.01) was observed for dietary intake of nitrosamines among Japanese men (highest versus lowest tertile odds ratio, 3.0; 95% CI, 1.4–6.4). An elevated risk for nitrosamines was not statistically significant among Japanese women (highest versus lowest tertile odds ratio, 1.9; 95% CI, 0.6–5.8). Estimated intake of nitrosamines was unrelated to cancer of the urinary tract among Caucasian men or women. [The interaction between nitrite and vitamin C or other inhibitors of nitrosation was not evaluated.]

The population-based case–control study of bladder cancer from Iowa, USA (Ward *et al*., 2003; see Section 2.4.1 (*c*)), also estimated dietary intake of nitrite. When quartiles of intake were analysed, no significant association with bladder cancer was observed among men or women (odds ratio for men, 1.2; 95% CI, 0.9–1.6 for ≥ 1.39 versus < 0.81 mg nitrite per day; odds ratio for women, 1.0; 95% CI, 0.7–1.6 for > 0.98 versus < 0.58 mg nitrite per day).

2.5 Genital and breast cancer

2.5.1 *Ingested nitrate*

(a) Ecological studies

Ecological studies of exposure to nitrate in Europe have evaluated regional concentrations of nitrate in the drinking-water in relation to mortality from or incidence rates of testicular, penile, prostatic and breast cancer. These are described in greater detail in Section 2.4 and are summarized in Table 2.5.

In northern Jutland, Denmark, incidence rates (age-standardized to the European standard population) of cancers of the male genital organs, uterus and other female genital organs were computed for Aalborg, a town that had high levels of nitrate in the water, and Aarhus, a town that had low levels. Incidence rates (per 100 000 persons) for cancers of the uterus (cervix and corpus combined) were 44% higher in Aalborg, but no significant differences were observed in the rates of other cancers (Jensen, 1982).

A study in Valencia, Spain (Morales-Suárez-Varela *et al*., 1995), examined mortality rates (directly age-standardized [standard population unspecified]) for prostatic cancer (ICD-9 185) which were similar across exposure categories: 16.9, 16.9 and 24.04 [per 100 000 person–years].

(b) Cohort study

The US Iowa Women's Health Study (Weyer *et al*., 2001) examined nitrate in both the diet and drinking-water in relation to the incidence of breast, ovarian and corpus uterine cancers (summarized in Table 2.6). No association was apparent between cancers of the breast, uterine corpus or ovary and dietary levels of nitrate. When average levels of nitrate in water (all years) were used, relative risks were increased non-significantly for

ovarian cancer (relative risk, 1.84; 95% CI, 0.88–3.84), reduced for cancer of the uterine corpus (relative risk, 0.55; 95% CI, 0.33–0.92) and close to unity for breast cancer (relative risk, 1.03; 95% CI, 0.83–1.28). Use of private wells was more weakly related to ovarian cancer (relative risk, 1.55; 95% CI, 0.77–3.13) and appeared to be unrelated to cancers of the breast or uterine corpus. Relative risks for nitrate in water and use of private wells were adjusted for multiple potentially confounding factors. [There was no assessment of potential effect modification, i.e. by vitamin C intake.]

(c) Case–control studies

(i) *Endometrial cancer*

A hospital/clinic-based case–control study (Barbone *et al*., 1993; see Table 2.7) of endometrial cancer that was conducted in Birmingham, Alabama, USA, examined dietary intake of nitrate and included 103 women who were newly diagnosed with histologically confirmed endometrial cancer from June 1985 to December 1988 and were identified from the University of Alabama Hospital and a large private gynaecology–oncology practice in Birmingham. Controls were 236 women with an intact uterus matched on age and race who had attended the University optometry clinic. Information on reproductive history, medical history, anthropometric measurements and other factors was elicited through an in-person interview. Cases and controls also completed an interviewer-administered food-frequency questionnaire (the Nurses' Health Study 116-item questionnaire). Response rates were 93% for cases overall of whom 61% completed the nutritional assessment and 77% for controls overall of whom 71% completed the nutritional assessment. Dietary intake of nitrate was inversely related to the risk for endometrial cancer (odds ratio, 0.4; 95% CI, 0.2–0.8 in the highest versus lowest tertile of nitrate). These results were adjusted for age, race, years of schooling, total calories, use of unopposed estrogens, obesity, shape of obesity, tobacco smoking, age at menarche, age at menopause, number of pregnancies, diabetes and hypertension and changed only slightly with further adjustment for potassium (odds ratio, 0.5; 95% CI, 0.2–0.9).

(ii) *Testicular cancer*

Exposure to nitrate in relation to the incidence of testicular cancer was examined in a population-based case–control study in Denmark (Møller, 1997; see Table 2.7). Cases were 514 men (239 non-seminoma, 262 seminoma) who were born between 1916 and 1970 and were diagnosed with testicular cancer from 1986 to 1988. Controls were 720 men randomly sampled from the Danish population and frequency-matched on year of birth. Participants were interviewed by telephone. Of the cases approached, 88% participated, which represents 74% of the total incident cases in Denmark. Among controls, 69% of those approached took part in the study. The study assessed being born or living during childhood in areas known to have high groundwater levels of nitrate from manure and agricultural fertilizers. These regions included Aarhus, Viborg and Nordylland counties. In 1994, 22% of the waterworks in these areas contained more than 25 mg/L nitrate compared with 6% for the rest of the country. Odds ratios were slightly

increased among men born in the area that had high levels of nitrate (odds ratio, 1.27; 95% CI, 0.99–1.64); risk estimates were similar for both non-seminoma and seminoma tumours. The association was stronger for men who had lived in the area that had high levels of nitrate for the larger part of their childhood (odds ratio, 1.40; 95% CI, 1.09–1.81); again, the magnitude of the risk estimates were comparable for both histological types of tumour. The association appeared to be limited to men who had lived in the area that had high levels of nitrate during childhood but who did not live in the country (odds ratio for men who did not live in the country, 1.51; 95% CI, 1.03–2.20; odds ratio for men who lived in the country, 1.10; 95% CI, 0.79–1.53). [In light of the heterogeneity in nitrate in the exposure groups, and lack of consistency between the results for urban versus rural residence, the results argue against the association being related to nitrates.]

2.5.2 *Nitrite*

No cohort or case–control studies of have examined genital or breast cancers in relation to ingested nitrites.

2.6 Leukaemia and lymphoma

2.6.1 *Ingested nitrate*

(a) Ecological studies

Two ecological studies of levels of nitrate in the drinking-water and non-Hodgkin lymphoma were conducted in North America. Weisenburger *et al*. (1987) reported a twofold higher incidence of non-Hodgkin lymphoma among 25 counties in Nebraska where 20% or more of the private wells contained levels of nitrate-N greater than 10 mg/L compared with 25 counties where fewer than 10% of wells contained this level. A Canadian study (Van Leeuwen *et al*., 1999) (described in detail in Section 2.2) in 40 districts of Ontario evaluated the incidence of non-Hodgkin lymphoma in relation to levels of nitrate (weighted means of the levels in public and private wells). Incidence rates for non-Hodgkin lymphoma were not associated with the level of nitrate (range, 0.05–7.79 mg/L). The study also evaluated levels of atrazine, a crop herbicide that was weakly associated with higher rates of non-Hodgkin lymphoma among men but not among women.

Three ecological studies in Europe that evaluated levels of nitrate in drinking-water from public water supplies and the incidence of non-Hodgkin lymphoma had mixed results. A study in the agricultural district of Trnava, Slovakia (Gulis *et al*., 2002) (described in detail in Section 2.2) found a significant positive trend ($P = 0.021$) in incidence rates for non-Hodgkin lymphoma among men and women with increasing levels of nitrate in public water supplies (categories of nitrate: 0–< 2.3, 2.3–4.5, > 4.5 mg/L nitrate-N). Levels of nitrate were averaged over 20 years (1975–95) and incidence was calculated for the years 1986–95. An ecological study in the United

Kingdom (Law *et al*., 1999) evaluated levels of nitrate in 1990–95 (mean of monthly averages in water supply zones with homogeneous levels of nitrate and a population of < 50 000) in relation to the incidence of non-Hodgkin lymphoma in 1984–93 adjusted for population density. Overall, incidence was not related to levels of nitrate; however, incidence in 1984–88 (but not 1989–93) was positively associated with the average level of nitrate. [The authors interpreted the inconsistent association in the two time periods as not supportive of the hypothesis that levels of nitrate in the drinking-water are associated with non-Hodgkin lymphoma.] An ecological study in Sardinia, Italy (Cocco *et al*., 2003), compared incidence rates of non-Hodgkin lymphoma in 1974–93 with monitoring data on levels of nitrate in 1993 for 153 communes (median, 0.74 mg/L). There was no trend in the incidence of non-Hodgkin lymphoma among men or women by category of nitrate, although incidence rate ratios were significantly elevated for some categories of nitrate among men. Fifteen of the 153 communes had data on nitrate in 1971–84 when levels were higher (median, 1.83 mg/L); these higher levels of nitrate (≥ 5.7 versus < 1.81 mg/L) were not associated with incidence rates among men or women either.

One ecological study in Southwest England, United Kingdom (Foster *et al*., 1997), evaluated incidence (1984–88) of leukaemia subtypes and myelodysplasias in relation to levels of nitrate in public water supplies (46 water supply zones). The specific diagnostic groups that were evaluated included acute myeloblastic leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia, myelproliferative disorders and myleodysplasias. No significant differences in SIRs were observed for any of the leukaemias, myeloproliferative disorders or myleodysplasias in relation to levels (1984–88) of nitrate in public water supplies (range, 0–18.6 mg/L; weighted mean, < 10 mg/L; measurements in three of the 46 water supply zones exceeded 10 mg/L).

One study in 65 counties in China (Wu *et al*. 1993) (described in detail in Section 2.2) evaluated urinary levels of nitrate, 'nitrosation potential' (decrease in urinary NPRO after feeding ascorbic acid) measured by the NPRO test and excretion of *N*-nitroso amino acids among men aged 35–64 years in relation to mortality rates (ages, 0–64 years in 1973–75) for leukaemia. Mortality rates were significantly positively correlated with urinary excretion of nitrate, nitrosation potential and the sum of the *N*-nitroso amino acids.

(b) Cohort and case–control studies

A cohort study of women in Iowa (Weyer *et al*., 2001) (described in detail in Section 2.4.1) evaluated levels of nitrate in drinking-water from public supplies and dietary intake of nitrate. The water source at the current home was assessed in 1989 and cancer incidence was evaluated from the period of enrolment in 1986 through to 1998 (Table 2.8). The average level of nitrate was calculated from public monitoring data in 1955–88 for women who had used the same water supply for 10 or more years (396 towns/cities). Risk was also evaluated among women who used private wells in 1989, although no measurements of nitrate were available. In models adjusted for confounding factors that included intake of fruit and vegetables, intake of vitamins C and E, body mass index, education, physical activity and tobacco smoking, no significant

Table 2.8. Cohort study of nitrate in the drinking-water and nitrate and leukaemia and lymphoma

Reference, study location, study period	Organ site (ICD code)	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weyer *et al*. (2001), Iowa, USA; 1986–98	Leukaemia	Cohort of 21 977 Iowa women, 55–69 years of age in 1986, who had a valid driver's licence and no previous history of cancer and who used the same water supply for > 10 years (87% > 20 years), 1986–98 linked to the Iowa Cancer Registry; response rate, 43%	Mailed baseline questionnaire in 1986 included tobacco smoking and other factors and a 126-item food-frequency questionnaire(adapted from the 1984 version of the Nurses' Health Study); a follow-up questionnaire in 1989 included type of water system of current residence and duration of use	**Average nitrate (mg/L nitrate-N) 1955–88**			Average nitrate: age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, vitamin C, E, diet nitrate, fruit and vegetables; nitrate in the diet: age, total energy	Nitrite in diet or interaction with vitamin C or smoking not evaluated
				< 0.36	31	1.0 (reference)		
				0.36–1.00	27	0.85 (0.49–1.47)		
				1.01–2.46	23	0.71 (0.39–1.29)		
				> 2.46	24	0.55 (0.29–1.04)		
				Nitrate in the diet (mg N/day)				
				< 11.6	37	1.0 (reference)		
				11.6–18.0	34	0.88 (0.55–1.40)		
				18.1–27.2	25	0.62 (0.37–1.04)		
				> 27.2	38	0.91 (0.56–1.46)		
	Non-Hodgkin lymphoma (200, 202)			**Average nitrate (mg/L nitrate-N) 1955–88**				
				< 0.36	27	1.0 (reference)		
				0.36–1.00	24	0.86 (0.48–1.55)		
				1.01–2.46	12	0.44 (0.20–0.95)		
				> 2.46	31	1.12 (0.61–2.06)		
				Nitrate in the diet (mg N/day)				
				< 11.6	22	1.0 (reference)		
				11.6–18.0	28	1.28 (0.73–2.24)		
				18.1–27.2	23	1.07 (0.59–1.94)		
				> 27.2	37	1.73 (1.00–3.00)		

CI, confidence interval; ICD, International Classification of Diseases

relationship was observed between average levels of nitrate in public supplies (median, 1.0 mg/L nitrate-N; interquartile range, 0.36–2.46 mg/L nitrate-N) and risk for leukaemia (94 cases) or non-Hodgkin lymphoma (105 cases). The relative risk for non-Hodgkin lymphoma decreased with increasing quartiles of average nitrate. The investigators did not evaluate the interaction with vitamin C or other factors that affect nitrosation. Use of private wells (> 10 years in 1989) was not associated with risk for either cancer. There was no trend in risk with increasing quartiles of dietary nitrate (highest quartile, > 27 mg per day), although the relative risk for leukaemia was marginally significant (1.73; 95% CI, 1.00–3.00).

The findings of case–control studies of nitrate in drinking-water and dietary intake of nitrate in relation to risk for non-Hodgkin lymphoma are summarized in Table 2.9. No case–control studies of other haematological malignancies have been conducted.

Three population-based case–control studies in the midwestern USA (Ward *et al*., 1996, 2006; Freedman *et al*., 2000) examined the relationship between average levels of nitrate in public water supplies over an average of 30 years and incident cases of non-Hodgkin lymphoma. The studies were similar in design, in that a history of source of residential water was collected and linked to data from public supply monitoring carried out by each town. The size of the population of the large majority of towns was < 50 000 and each study included over 100 utilites. Levels of nitrate were not monitored every year (the earliest year was 1935 for studies in Iowa and 1947 for the study in Nebraska) and values for missing years were imputed using weights based on the number of years since a measurement of nitrate. Data on measurements were most frequent by available after 1960. All studies evaluated potential confounding factors and analyses were limited to the populations who had spent 70–90% of their person–years in an area that had an estimate of nitrate during the exposure period to reduce misclassification by unknown (and probably higher) levels of nitrate from private wells. Two of the studies (Ward *et al*., 1996, 2006) also evaluated measurements of nitrate in private wells. These studies also assessed dietary intake of nitrate using a food-frequency questionnaire and a database developed from published values for nitrate in foods.

Ward *et al*. (1996) linked 156 cases of non-Hodgkin lymphoma and 527 controls to the average level of nitrate in public water supplies in 1947–84 in eastern Nebraska, USA. The population for these analyses was limited to people who had spent 90% or more of their person–years in the exposure period in an area that had an estimate of nitrate. The median exposure was 1.8 mg/L nitrate-N (interquartile range, 1.7–3.8 mg/L). Increasing quartiles of average nitrate were associated with an increasing risk for non-Hodgkin lymphoma and risk was elevated in the highest quartile for both men and women. Another measurement of exposure (years with a supply ≥ 10 mg/L nitrate-N versus no years at this level) was associated with a 50% increased risk (95% CI, 1.0–2.2). Those exposed to ≥ 10 mg/L nitrate-N were generally exposed for a short time period (first and third quartiles of duration were 2 years) and the odds ratio decreased to 1.1 after adjustment for occupational use of organophosphate insecticides and family history of cancer. Usual intake of tap-water was assessed and intake of nitrate from drinking-water was calculated

Table 2.9. Case–control studies of nitrate in the drinking-water or nitrate and nitrite in the diet and non-Hodgkin lymphoma (ICD code 200, 202)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al*. (1996), 66 counties of eastern Nebraska, USA, 1983–86	385 cases (white men and women) from Nebraska Lymphoma Study Group (population-based ascertainment of cases from hospitals and pathology laboratories across the state), aged 21 years and older; 40% of interviews with next-of-kin; 100% histologically confirmed; response rate, 90% 1432 population-based controls selected by random-digit-dialling for living controls aged < 65 years or from Health Care Finance Administration files and Nebraska mortality files for deceased controls; frequency-matched by race, age, sex, vital status; additionally matched by year of death	Interview-administered standardized FFQ designed to evaluate major sources of dietary nitrate, nitrite and vitamin C; lifetime history of water source; monitoring data on nitrate in 1947–84 from 138 public utilities in Nebraska; imputation of values for years without data on nitrate; analyses of nitrate in drinking-water: 156 cases, 527 controls with ≥ 90% person–years after 1947 with estimates of nitrate	**Average nitrate (mg/L nitrate-N) in public supplies 1947–79**				No interaction with vitamin C intake; average level of nitrate in 1965–79 (odds ratio, 1.12; 95% CI, 1.00–1.25) associated with risk but not 1947–64 (odds ratio, 0.99; 95% CI, 0.89–1.10); both metrics of nitrate in water showed similar results for men and women; self-reported and proxies.
			Q1, < 1.6	21	1.0 (reference)	Age, gender, family history of cancer	
			Q2, 1.6–< 2.0	67	1.4 (0.8–2.5)		
			Q3, 2.0–< 4.0	19	1.5 (0.7–3.0)		
			Q4, ≥ 4.0	47	2.0 (1.1–3.6)		
			Average nitrate/ vitamin C				
			Q1/High vitamin C	5	1.0 (reference)	Age, gender	
			Q2/High vitamin C	12	1.5 (0.5–4.6)		
			Q3/High vitamin C	11	1.4 (0.5–4.6)		
			Q4/High vitamin C	15	2.0 (0.7–6.1)		
			Q1/Low vitamin C	10	1.4 (0.4–4.5)		
			Q2/Low vitamin C	16	2.4 (0.8–7.4)		
			Q3/Low vitamin C	16	2.2 (0.7–6.7)		
			Q4/Low vitamin C	21	3.3 (1.1–9.9)		
			Dietary nitrate (mg N/day)			Age, gender, family history of cancer, vitamin C, carotenes	
			Q1, < 13	35	1.0 (reference)		
			Q2, 13–< 19	38	1.1 (0.6–2.0)		
			Q3, 19–26	20	0.8 (0.4–1.7)		
			Q4, > 26	11	0.7 (0.3–1.9)		
			Dietary nitrite (mg/day)			Results in text only for Q4 versus Q1, adjustment factors not stated	
			Q4 versus Q1		0.9 (0.5–1.7)		

Table 2.9 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Freedman *et al.* (2000), Minnesota, USA, excluding residents of the four largest cities, 1980-82	329 cases (white men) ascertained from Minnesota hospital and pathology laboratory records, aged ≥ 30 years; 100% histologically confirmed; response rate, 89% (reported in Cantor *et al.*, 1992) 642 population-based controls (white men), and selected by random-digit dialling for ages < 65, a 1% random listing from Medicare files for living subjects aged 65 years and older and state death certificates for deceased cases; frequency-matched by age, vital status, state of residence	Interview-administered standardized questionnaire; lifetime history of water source; monitoring data on nitrate from 157 public utilities 1947–80; imputation of missing data (same method as Ward *et al*., 1996); analysis of nitrate: 73 cases, 147 controls with ≥ 90% person–years after 1947 with estimates of nitrate	**Average nitrate (mg/L nitrate-N) in public supplies 1947–75** ≤ 0.05 > 0.5–≤ 1.5 > 1.5	 41 19 3	 1.0 (reference) 1.4 (0.7–2.5) 0.3 (0.1–0.9)	Age	Exposure range, 0.1–7.2 mg/L nitrate-N; no differences for proxy/self-respondents

Table 2.9 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al.* (2006), Iowa, USA, 1998–2000	361 cases from Iowa Cancer Registry, aged 20–74 years; 100% histologically confirmed; response rate, 67% 276 population-based controls selected by random-digit dialling for ages < 65 and from Medicare eligibility files for ages 65–74 years; frequency matched by age, centre, race, gender	Interview-administered standardized questionnaire; complete history of water source; monitoring data on nitrate from public utilities and sample from private well at time of interview; analysis of nitrate: 181 cases, 142 controls with ≥ 70% person–years 1960 onwards with nitrate estimates; self-administered dietary questionnaire; modified version of Block FFQ with additional questions about high nitrate vegetables and processed meats	**Average nitrate (mg/L nitrate-N) in public supplies, 1960–2000** ≤ 0.63 0.63–1.36 1.37–2.89 ≥ 2.90 **Average nitrate in water (mg/day)/ vitamin C (mg/day)** High vitamin C/ < 3 mg nitrate Low vitamin C/ < 3 mg nitrate High vitamin C/ ≥ 3 mg nitrate Low vitamin C/ ≥ 3 mg nitrate	 40 49 46 46 31 38 13 13	 1.0 (reference) 1.3 (0.7–2.4) 1.0 (0.5–1.9) 1.2 (0.6–2.2) 1.0 (reference) 1.1 (0.5–2.3) 2.3 (0.7–7.0) 2.0 (0.6–5.9)	Age, sex, education	Intake of tap-water did not modify association; no significant interaction with vitamin C (<90 mg/day; ≥90 mg/day), red meat, cured meat, smoking status. Among subgroup with estimates of nitrate in water and diet, nitrate in water contributed a median of 13% (men) and 11% (women) towards total intake of nitrate.

Table 2.9 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al.* (2006) (contd)			**Nitrate in the diet (mg/day)**			Age, sex, education, study centre, race, dietary vitamin C, total energy	
			< 76	159	1.0 (reference)		
			76–113.9	116	0.75 (0.51–1.10)		
			114–169.9	111	0.71 (0.47–1.07)		
			≥ 170	80	0.54 (0.34–0.86)		
			Nitrite in the diet (mg/day)				
			< 0.71	82	1.0 (reference)		
			0.71–0.909	108	1.5 (1.0–2.3)		
			0.91–1.209	110	1.7 (1.1–2.7)		
			≥ 1.21	166	3.1 (1.7–5.5)		
			Nitrite in the diet from animal sources (mg/day)				
			< 0.16	101	1.0 (reference)		
			0.16–< 0.26	106	1.0 (0.7–1.5)		
			0.26–< 0.42	123	1.0 (0.7–1.6)		
			≥ 0.42	136	1.0 (0.6–1.7)		

CI, confidence interval; ICD, International Classification of Diseases; FFQ, food frequency questionnaire; Q, quartile

(in milligrams per day). Risks were higher among people who had a higher intake of nitrate from water (≥ 6.3 mg nitrate-N per day) and an intake of vitamin C below the median (< 130 mg per day) (odds ratio, 3.3; 95% CI, 1.1–9.9) compared with people whose intake of nitrate was < 2.5 mg nitrate-N per day and whose vitamin C intake was above the median; however, the statistical test for interaction was not significant. Increasing dietary intake of nitrate that came primarily from vegetables was associated with decreasing risks for non-Hodgkin lymphoma. Adjustment for vitamin C and carotenes attenuated the association and the inverse associations were not statistically significant.

Freedman *et al*. (2000) linked the average level of nitrate in Minnesota, USA, in 1947–75 (exposure was lagged 10 years) to 73 cases and 147 controls who lived in an area that had an estimate of nitrate for 90% of their person–years during the exposure period. Average levels of nitrate were low (highest exposure category, > 1.5 mg/L nitrate-N; median in this category, 2.4 mg/L nitrate-N) and were not associated with increasing risk; there was a significant inverse association for the highest category compared with ≤ 0.05 mg/L.

Ward *et al*. (2006) evaluated several indices of exposure to nitrate in Iowa, USA, including the average level of nitrate in 1960–2000 and the number of years that a public water supply with levels of nitrate ≥ 5 and ≥ 10 mg/L nitrate-N was used for 181 cases and 142 controls who lived in areas that had estimates of nitrate for 70% or more of their person–years during the exposure period. Increasing quartiles of the average level of nitrate were not associated with risk for non-Hodgkin lymphoma (median, 1.4; interquartile range, 0.6–2.9). Ten or more years of use of public supplies that had levels of > 5 mg/L nitrate-N was associated with a non-significant increased risk compared with no years of exposure at this level (odds ratio, 1.4; 95% CI, 0.7–2.9). One or more years of use of a supply that contained ≥ 10 mg/L nitrate-N was associated with a slight decrease in risk (odds ratio, 0.6; 95% CI, 0.2–1.5); exposure at or above this level was infrequent (11 cases, 10 controls). Levels of nitrate were measured in private wells at the time of the interview; 54 cases and 41 controls had used the well as their primary source of drinking-water for 5 or more years. Among this group, exposure levels were generally low; only eight cases and eight controls had levels of nitrate that were 5 mg/L nitrate-N or greater. Compared with those who had no detectable nitrate (< 0.2 mg/L nitrate-N), there was no association between levels of nitrate in private wells and risk for non-Hodgkin lymphoma (< 5 mg/L nitrate-N odds ratio, 1.7; 95% CI, 0.6–5.2; ≥ 5 mg/L nitrate-N odds ratio, 0.8; 95% CI, 0.2–2.5). For approximately half the study population, dietary intake was assessed using a 117-item food-frequency questionnaire that included questions about vegetables rich in nitrate and processed meats. Usual intake of nitrate from tap-water was also estimated. Among the subgroup that had estimates of nitrate from water and diet, nitrate from water contributed a median of 13% (men) and 11% (women) towards total intake of nitrate. Increasing quartiles of dietary intake were associated with an inverse risk for non-Hodgkin lymphoma after adjustment for dietary intake of vitamin C, education and study matching factors (age, sex, race and centre).

2.6.2 *Ingested nitrite*

Dietary nitrite was assessed in two case–control studies (Ward *et al*., 1996, 2006; Table 2.9). Quartiles of dietary nitrate were not associated with risk for non-Hodgkin lymphoma in the first study. Only the odds ratio for the highest versus the lowest quartiles were presented and no cut-off points were given (Ward *et al*., 1996). In the second study, quartiles of nitrite intake were significantly associated with an increasing risk for non-Hodgkin lymphoma; however, when animal and plant sources of nitrite were evaluated separately, the association was due only to plant and not to animal sources of nitrite (Ward *et al*., 2006). [The authors interpreted these findings as not supportive of a role for nitrite *per se* because animal sources of nitrite would be expected to show a stronger association with risk according to the nitrosation hypothesis.]

2.7 Oral, pharyngeal and laryngeal cancers

2.7.1 *Ingested nitrate*

A cohort study of head and neck cancers in Finland (Knekt *et al*., 1999) (described in detail in Section 2.2.1) estimated dietary intake of nitrate from a food-frequency questionnaire and a Finnish nutrient database (Table 2.10). Quartiles of dietary nitrate were not associated with an increased risk (48 cases).

Dietary intake of nitrate was evaluated in relation to oral and laryngeal cancers in one case–control study (Rogers *et al*., 1995) (described in detail in Section 2.2.1) which included 351 cases of oral cancer and 169 cases of laryngeal cancer in the Seattle metropolitan area in the USA (Table 2.11). Levels of nitrate were estimated from a 125-item food-frequency questionnaire and were linked to a database developed from the published literature. Tertiles of dietary intake of nitrate (highest tertile, > 226 mg per day [51 mg per day as nitrate-N]) were associated with significant inverse trends in the risk for oral ($P = 0.001$) and laryngeal ($P = 0.005$) cancers.

2.7.2 *Ingested nitrite*

The cohort study in Finland (Knekt *et al*., 1999) found no association between increasing quartiles of dietary nitrite and head and neck cancers, nor was NDMA intake associated with risk.

Tertiles of dietary intake of nitrite were not associated with the risk for oral or laryngeal cancers in the case–control study by Rogers *et al*. (1995); the odds ratios for the highest tertiles were below 1 (oral cancer, 0.66; 95% CI, 0.39–1.12; laryngeal cancer, 0.67; 95% CI, 0.34–1.34) (Table 2.11). The authors evaluated dietary intake of nitrate by level of vitamin C intake (> 195 versus < 195 mg per day) and by consumption of tea (less than once a week versus more than once a week), which are factors that inhibit endogenous nitrosation. Among persons who had a higher dietary intake of nitrate and lower consumption of either vitamin C or tea, no elevated risk was observed compared with

Table 2.10. Cohort studies of nitrate in the drinking-water and nitrate and nitrite in the diet and various cancers

Reference, study location, period	Organ site (ICD code)	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Knekt *et al.* (1999), several regions of Finland, 1966–72	Head and neck (140–148, 150, 161) (n = 48)	Cohort of 9985 persons with no cancer screened by the mobile health clinic of the Social Insurance Institution in several regions; cancer incidence follow-up through the Finnish Cancer Registry to 1990	FFQ; nitrate, nitrite, levels of NDMA estimated from a Finnish database (see Dich *et al.*, 1996 for more details of estimations of nitrate and nitrite); reproducibility estimated at intervals of 4–8 months with intraclass correlation coefficient: 0.48, nitrate; 0.73, nitrite; 0.53, NDMA; and 0.36, 0.25, 0.26, respectively for long-term reproducibility (4–7 years)	**Nitrate in the diet**			Age, sex, municipality, smoking, and energy intake	NDMA intake (Q2 versus Q1: odds ratio, 2.82; 95% CI, 1.11–7.11)
				Q1		1.0 (reference)		
				Q2		0.72 (0.32–1.60)		
				Q3		0.50 (0.21–1.20)		
				Q4		0.84 (0.39–1.81)		
				P for trend		0.95		
				Nitrite in the diet				
				Q1		1.0 (reference)		
				Q2		0.46 (0.19–1.12)		
				Q3		0.76 (0.35–1.66)		
				Q4		0.83 (0.36–1.88)		
				P for trend		0.77		
	Colorectum (153, 154) (n = 73)			**Nitrate in the diet**				NDMA intake (Q2 versus Q1: odds ratio, 2.12; 95% CI, 1.04–4.33)
				Q1		1.0 (reference)		
				Q2		1.01 (0.52–1.92)		
				Q3		0.98 (0.51–1.87)		
				Q4		1.04 (0.54–2.02)		
				P for trend		0.64		
				Nitrite in the diet				
				Q1		1.0 (reference)		
				Q2		0.82 (0.45–1.48)		
				Q3		0.94 (0.50–1.78)		
				Q4		0.74 (0.34–1.63)		
				P for trend		0.45		

Table 2.10 (contd)

Reference, study location, period	Organ site (ICD code)	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weyer *et al*. (2001), Iowa, USA; 1986–98	Lung and bronchus	Cohort of 21 977 Iowa women, 55–69 years of age in 1986, who had a valid driver's licence and no previous history of cancer and who used the same water supply for > 10 years (87% > 20 years), 1986–98 linked to the Iowa Cancer Registry; response rate, 43%	Mailed baseline questionnaire in 1986 included tobacco smoking and other factors and a 126-item food-frequency questionnaire(adapted from the 1984 version of the Nurses' Health Study); a follow-up questionnaire in 1989 included type of water system of current residence and duration of use	**Average nitrate (mg/L nitrate-N) 1955–88**			Average nitrate: age, education, smoking, physical activity, body mass index, waist-to-hip ratio, total energy, vitamin C, E, diet nitrate, fruit and vegetables; nitrate in the diet: age, total energy	Nitrite in diet or interaction with vitamin C or smoking not evaluated
				< 0.36	56	1.0 (reference)		
				0.36–1.00	57	1.00 (0.67–1.47)		
				1.01–2.46	77	1.49 (1.02–2.17)		
				> 2.46	47	0.83 (0.53–1.30)		
				Nitrate in the diet (mg N/day)				
				< 11.6	76	1.0 (reference)		
				11.6–18.0	65	0.85 (0.61–1.19)		
				18.1–27.2	66	0.87 (0.62–1.22)		
				> 27.2	59	0.78 (0.55–1.11)		
	Colon			**Average nitrate (mg/L nitrate-N) 1955–88**				
				< 0.36	58	1.0 (reference)		
				0.36–1.00	86	1.53 (1.09–2.16)		
				1.01–2.46	92	1.54 (1.08–2.19)		
				> 2.46	64	0.98 (0.66–1.46)		
				Nitrate in the diet (mg N/day)				
				< 11.6	98	1.0 (reference)		
				11.6–18.0	78	0.79 (0.59–1.07)		
				18.1–27.2	90	0.93 (0.69–1.24)		
				> 27.2	97	1.00 (0.74–1.34)		

Table 2.10 (contd)

Reference, study location, period	Organ site (ICD code)	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weyer *et al*. (2001) (contd)	Rectum			**Average nitrate (mg/L nitrate-N) 1955–88**				
				< 0.36	33	1.0 (reference)		
				0.36–1.00	25	0.72 (0.41–1.25)		
				1.01–2.46	32	0.95 (0.56–1.62)		
				> 2.46	16	0.47 (0.24–0.92)		
				Nitrate in the diet (mg N/day)				
				< 11.6	28	1.0 (reference)		
				11.6–18.0	39	1.42 (0.87–2.31)		
				18.1–27.2	27	1.01 (0.59–1.73)		
				> 27.2	28	1.06 (0.61–1.83)		
	Pancreas			**Average nitrate (mg/L nitrate-N) 1955–88**				
				< 0.36	17	1.0 (reference)		
				0.36–1.00	13	0.88 (0.42–1.84)		
				1.01–2.46	20	1.45 (0.73–2.88)		
				> 2.46	11	0.64 (0.27–1.56)		
				Nitrate in the diet (mg N/day)				
				< 11.6	19	1.0 (reference)		
				11.6–18.0	15	0.79 (0.40–1.56)		
				18.1–27.2	16	0.86 (0.44–1.69)		
				> 27.2	19	1.02 (0.52–1.99)		

Table 2.10 (contd)

Reference, study location, period	Organ site (ICD code)	Cohort description	Exposure assessment	Exposure categories	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Weyer *et al*. (2001) (contd)	Oesophagus, stomach, small intestine, liver and bile ducts, gall-bladder, peritoneum/ retroperito-neum, other digestive			**Average nitrate (mg/L nitrate-N) 1955–88**				
				< 0.36	11	1.0 (reference)		
				0.36–1.00	12	1.39 (0.58–3.30)		
				1.01–2.46	16	1.83 (0.78–4.31)		
				> 2.46	16	2.09 (0.88–4.94)		
				Nitrate in the diet (mg N/day)				
				< 11.6	17	1.0 (reference)		
				11.6–18.0	19	1.18 (0.61–2.27)		
				18.1–27.2	20	1.32 (0.68–2.57)		
				> 27.2	15	1.03 (0.50–2.13)		

CI, confidence interval; FFQ, food-frequency questionnaire; ICD, International Classification of Diseases; NDMA, *N*-nitrosodimethylamine; Q, quartile

Table 2.11. Case–control studies of nitrite and nitrate in drinking-water and the diet and lung, nasopharyngeal, oral and laryngeal cancer

Reference, study location, period	Organ site	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Goodman *et al.* (1992), Oahu, Hawaii, USA, 1983–85	Lung cancer	362 cases (226 men, 100 women), aged 30–84 years, residents of Oahu in five ethnic groups (Caucasian, Chinese, Japanese, Filipino, Hawaiian) identified by Hawaii Tumor Registry and diagnosed at seven major civilian hospitals; 100% histologically confirmed; response rates, 70% (men) and 63% (women) 865 population-based controls and selected by random-digit dialling (1983–84); random sample of participants of Oahu survey (refusals < 5%); supplemented controls > 65 with health care financing administration sample; matched by age, sex; response rates, 71% (men) and 67% (women)	In-person interview using standardized questionnaire; 130-item FFQ validated for this study population; data sources for nitrite, nitrate and NDMA not specified	**Nitrite in the diet (μg/week)** *Men* < 2000 2000–< 4000 4000–< 7000 > 7000 *P* for trend *Women* < 2000 2000–< 4000 4000–< 7000 > 7000 *P* for trend		 1.0 (reference) 1.2 (0.6–2.3) 1.7 (0.9–3.3) 2.0 (1.0–3.8) 0.02 1.0 (reference) 0.6 (0.2–1.2) 0.9 (0.4–2.1) 1.5 (0.5–4.1) 0.22	Age, ethnicity, smoking, β-carotene	Results consistent across ethnic groups; stronger associations (men) with cured meats among current versus past smokers; heavier smokers, squamous-cell versus adenocarcinoma; NDMA associated with stronger increased risks among men and women (*p* for trend: men, < 0.001; women, 0.04); dietary nitrate inversely associated with risk [data not shown]; 86% of intake from vegetables

Table 2.11 (contd)

Reference, study location, period	Organ site	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
De Stefani *et al.* (1996), Montevido, Uruguay, 1994–95	Lung cancer	320 cases (307 men, 13 women) from participating hospitals, all ages; average age, 63.1 years; histologically confirmed; response rate, 100% 320 hospital controls excluding diseases related to tobacco use; most frequent conditions: fractures (36%), eye disorders (22%), abdominal hernia (15%), trauma (9%), appendicitis (5%); frequency-matched by age, sex, hospital, residence (Montevideo, other counties); response rate, 100%	Interview-administered standardized questionnaire; 70-item FFQ focusing on main sources of nitrite, NDMA	**Dietary NDMA (μg/day)** ≤ 0.13 0.14-0.18 0.19-0.26 ≥ 0.27		 1.0 (reference) 0.88 (0.53–1.48) 1.77 (1.06–2.96) 3.14 (1.86–5.29)	Age, gender, residence, urban/rural status, family history of lung cancer, pack–years of tobacco smoking, total energy intake	Increasing risk with quartiles of NDMA for squamous-cell, small-cell and adeno-carcinoma; strongest association for squamous-cell and adenocarcinoma; dietary nitrite was estimated but results were not presented.

Table 2.11 (contd)

Reference, study location, period	Organ site	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Ward *et al.* (2000), Taipei, Taiwan, China, 1991–94	Nasopharynx	375 cases identified from 2 referral hospitals in Taipei, aged < 75 years; 100% histologically confirmed; response rate, 99% of cases and 47% of mothers 327 population-based selected from national household registration system; matched by township/district, age, sex; response rate, 88% of controls and 63% of mothers	In-person interviews of cases and controls and their mothers; mothers asked about child's diet at age 10 and 3 years, and during weaning, and mother's diet during breast-feeding; cases and controls asked about diet as adult and age 10 years; nitrate, nitrite and nitrosamine levels (semi-quantitative) estimated from published values for Chinese foods and, when no values were available, from western foods	***Nitrite from soya bean products** Q1 (low) Q2 Q3 Q4 (high) ***Nitrite from other foods** Q1 (low) Q2 Q3 Q4 (high)	 NR NR NR NR NR NR NR NR	 1.0 (reference) 0.6 (0.2–1.3) 0.5 (0.2–1.1) 0.6 (0.3–1.4) 1.0 (ref) 1.7 (0.6–4.9) 3.5 (1.3–9.5) 2.0 (0.7–6.0)	Age, gender, ethnicity, vegetable intake	Results for mother's reports of intakes at age 3 years and weaning were similar (based on fewer foods);* intake at age 10 years as reported by mothers; nitrosamine intake from foods other than soya beans (as estimated by mothers) at ages 10 and 3 years, and weaning was positively associated with risk (weaning Q4 odds ratio, 3.9; 95% CI, 1.4–10.4)

Table 2.11 (contd)

Reference, study location, period	Organ site	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Rogers *et al.* (1995), King, Snohomish and Pierce counties, Washington State, USA, 1983–87	Oral	351 cases from cancer surveillance system (part of NCI SEER); response rate, 73% (dietary component) 514 population-based controls selected by random-digit dialling; matched by age, gender; response rate, 76%	Personal interview; self-administered 125-item FFQ on foods high in nitrate, nitrite, NDMA; levels estimated from the published literature; nitrate in water estimated to be 1.3 mg/L	**Dietary nitrate (mg/day)** < 134 (T1) 134–226 (T2) > 226 (T3) *P* for trend **Dietary nitrite (mg/day)** < 1.06 (T1) 1.06–1.60 (T2) > 1.60 (T3) *P* for trend **Nitrite (mg)/ vitamin C** T1/high vitamin C T2/high vitamin C T3/high vitamin C T1/low vitamin C T2/low vitamin C T3/low vitamin C	 113 109 76 112 92 94 NR	 1.0 (reference) 0.66 (0.43–1.01) 0.46 (0.28–0.76) 0.001 1.0 (reference) 0.96 (0.61–1.51) 0.66 (0.39–1.12) 0.099 1.0 (reference) 1.62 1.01 2.40 1.64 1.30	All odds ratios adjusted for age, gender, education, pack–years of tobacco smoking, alcohol (drink–years), body mass index, total energy	No interaction of nitrite with vitamin C or tea consumption; NDMA tertiles associated with increasing risk (odds ratio highest versus lowest tertile, 1.82; 95% CI, 1.10–3.00) 95% CIs not given

Table 2.11 (contd)

Reference, study location, period	Organ site	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Rogers *et al.* (1995) (contd)	Larynx	169 cases from cancer surveillance system (part of NCI SEER)		**Dietary nitrate (mg/day)**				
				< 134 (T1)	67	1.0 (reference)		No interaction of nitrite with vitamin C, tea consumption; NDMA tertiles associated with increasing risk (odds ratio highest versus lowest tertile, 1.70; 95% CI, 0.91–3.18)
				134–226 (T2)	49	0.50 (0.29–0.88)		
				> 226 (T3)	35	0.42 (0.22–0.80)		
				P for trend		0.005		
				Dietary nitrite (mg/day)				
				< 1.06 (T1)		1.0 (reference)		
				1.06–1.60 (T2)		0.98 (0.54–1.79)		
				> 1.60 (T3)		0.67 (0.34–1.34)		
				P for trend		0.107		
				Nitrite/vitamin C	NR		Age, gender, smoking, alcohol, body mass index, education, energy intake	95% CIs not given
				T1/high vitamin C		1.0 (reference)		
				T2/high vitamin C		1.04		
				T3/high vitamin C		0.65		
				T1/low vitamin C		1.65		
				T2/low vitamin C		1.22		
				T3/low vitamin C		0.95		

CI, confidence interval; FFQ, food-frequency questionnaire; NCI SEER, National Cancer Institue Survey of Epidemiology End Results; NDMA, *N*-nitrosodimethylamine; NR, not reported; Q, quartile; T, tertile

persons who had a low intake of nitrite and high intake of vitamin C or tea (95% CIs were not provided). The authors also estimated dietary intake of NDMA, which was associated with an 82% significant increased risk for oral cancer and 70% non-significant increased risk for laryngeal cancer.

2.7.3 *Nitrate and nitrite in saliva*

A small hospital-based study in Italy (Airoldi *et al*., 1997), in which oral, pharyngeal and laryngeal cancers were combined (36 men), found no differences between concentrations of salivary nitrate, nitrite or *N*-nitroso compounds in cases and controls. Selection of controls was not specified in detail and it was indicated that they were often relatives of the cases.

Another small hospital-based study of oral cancer in Egypt (44 cases, 40 control volunteers) measured levels of nitrate and nitrite in saliva (Badawi *et al*., 1998). Higher levels of salivary nitrite were associated with an increased risk for oral cancer (odds ratio, 4.3; 95% CI, 1.4–13.3 for > 40 μg/mL nitrite). [Levels in cases may have been affected by the disease; the controls were not population-based and did not appear to be matched to the cases by gender or age. Therefore, it was not possible to ascertain if their salivary levels are representative of the population.]

2.8 Nasopharyngeal cancer

No studies have evaluated nitrate ingested from drinking-water or diet and the risk for nasopharygeal carcinoma (NPC).

2.8.1 *Ingested nitrite*

(a) Ecological studies

Two ecological studies (Wu *et al*., 1993; Yi *et al*., 1993) in areas of China where mortality from NPC was both high and low (rates for other cancers varied) used the NPRO test to evaluate the hypothesis that higher endogenous nitrosation is associated with a higher risk for NPC. The study by Wu *et al*. (1993) (described in detail in Section 2.2) evaluated cancer mortality rates in 69 counties in relation to urinary nitrate, nitrosation potential and excretion of three *N*-nitroso amino acids in urine. Mortality rates (ages 0–64 years in 1973–75) for NPC were significantly positively correlated with urinary nitrate ($r = 0.28$, $P < 0.05$) and one *N*-nitroso amino acid ($r = 0.26$, $P < 0.05$) but not with nitrosation potential ($r = 0.06$, $P > 0.05$).

Yi *et al*. (1993) evaluated endogenous nitrosation potential among men and women in high- ($n = 37$) and low-risk ($n = 40$) districts in Zangwu County, Gaungxi region in 1990. Incidence rates of NPC varied 10-fold across the districts. The methods used were similar to those of Wu *et al*. (1993) except that a baseline 12-h urine sample was collected to measure background levels of nitrate and *N*-nitroso amino acids after a normal evening

meal. Background levels did not differ between the two areas. Proline intake increased excretion of NPRO of people in the high-risk but not of those in the low-risk district.

(b) Case–control studies

One case–control study of NPC in Taiwan, China (Ward *et al*., 2000), estimated dietary intake of nitrate during adulthood and at ages 3 and 10 years and maternal diet during pregnancy and breast-feeding (Table 2.11). Levels of nitrite were determined from the published literature using values for Chinese foods when available and from other published sources (mainly Japanese, USA and European data). Both the study subjects and their mothers were asked about the subject's diet at age 10 years. Intake of nitrite was assessed across all foods and results were presented separately for nitrite intake from soya bean products and from other foods (preserved meats, salted fish, preserved vegetables) because soya beans contain inhibitors of nitrosation. Based on self-reported adult dietary intakes and those at age 10 years, neither intake of nitrite from soya beans nor that from other foods was significantly associated with the risk for NPC. Based on maternal reports of the subject's diet at age 10 years, age 3 years and during weaning, intake of nitrite from soya bean products was inversely associated with risk, whereas, increasing intake of nitrite from other foods was positively associated with risk after adjustment for potential confounders, including vegetable intake. Dietary intake of nitrosamines was also estimated from the published literature and a semiquantitative level was assigned to each food. The results were similar to those for nitrite. Intake of nitrosamines from soya bean products was inversely associated with risk, whereas that from other foods was positively associated with the childhood diet based on maternal reports.

2.9 Colon and rectal cancers

2.9.1 *Ingested nitrate*

(a) Ecological studies

Gulis *et al*. (2002) (described in detail in Section 2.2) found a positive correlation between levels of nitrate in public water supplies and the incidence of colon but not of rectal cancer in Slovakia. Elevated levels of nitrate in public water supplies in 40 'ecodistricts' of Ontario, Canada, were positively correlated with age-standardized incidence ratios for colon cancer among women ($P = 0.048$) (described in detail in Section 2.2). In multiple variable regression analyses, age-standardized incidence ratios in women were no longer significantly associated with levels of nitrate in the drinking-water (Van Leeuwen *et al*., 1999). In Spain (Morales-Suárez-Varela *et al*., 1995) (described in detail in Section 2.2), no correlation was observed between levels of nitrate in 258 municipalities in 1968 (towns grouped by average nitrate level: 0–< 5.7, 5.7–11, > 11 mg/L) and mortality rates for colon cancer in 1975–80.

The study by Wu *et al*. (1993) in 69 counties of China (described in detail in Section 2.2) found no significant correlation between mortality rates (ages 0–64 years in 1973–75) for colorectal cancer and urinary concentrations of nitrate ($r = 0.16$).

(b) Cohort and case–control studies

A cohort study in Finland (Knekt *et al*. 1999) (described in detail in Section 2.2) enrolled men and women who were screened at mobile health clinics in 1966–72 and estimated dietary intake of nitrate from a food-frequency questionnaire and a Finnish database (Table 2.10). The incidence of colorectal cancer assessed through to 1990 (73 cases) was not associated with quartiles of dietary intake of nitrate.

A cohort study (described in detail in Section 2.4) of women in Iowa, USA (Weyer *et al*., 2001), found an inverse association with long-term average levels of nitrate (1955–88) in the public water supplies that served the current residence (minimum duration, 11 years) and incidence of rectal cancer (Table 2.10). The highest quartile of the average level of nitrate was not associated with an increased risk for colon cancer; however, relative risks were significantly elevated in the second and third quartiles. The authors did not evaluate the interaction with vitamin C intake. Increasing quartiles of dietary intake of nitrate were not associated with risk for colon or rectal cancers.

A population-based case–control study of colon and rectal cancer in Iowa, USA (De Roos *et al*., 2003), included 685 cases of colon cancer, 655 cases of rectal cancer and 2434 controls. The analyses of drinking-water were limited to those who had spent 70% or more of their person–years (1960–87) in an area with estimated levels of nitrate in public water supplies (376 colon cancers, 338 rectal cancers, 1244 controls). Overall, no relationship was observed between average levels of nitrate (1960–87) and years with a supply with > 5 or > 10 mg/L nitrate-N and risk for either colon or rectal cancer (Table 2.12). The authors evaluated potential interactions between exposure to nitrate in the drinking-water and factors that may affect endogenous nitrosation in the stomach or colon including vitamin C intake, meat intake and history of inflammatory bowel disease. For colon cancer, significant positive interactions were observed between exposures for 10 or more years to levels of above 5 mg/L nitrate-N and low vitamin C and high meat intake. Similar results were found for the metrics of nitrate in water. Quartiles of dietary intake of nitrate estimated from a food-frequency questionnaire and published levels in foods were inversely associated with risk for colon cancer and no association with rectal cancer was observed.

2.9.2 *Ingested nitrite*

A cohort study in Finland (Knekt *et al*., 1999) and a case–control study of colon and rectal cancer in Iowa, USA (De Roos *et al*., 2003), evaluated dietary intake of nitrite (Tables 2.10 and 2.12). Knekt *et al*. (1999) estimated dietary intake of both nitrite and NDMA. The incidence of colorectal cancer (73 cases) was not associated with increasing quartiles of dietary nitrite intake. However, the highest quartile of intake of NDMA was

Table 2.12. Case–control study of nitrate in drinking-water and nitrate and nitrite in the diet and colon and rectal cancers

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
De Roos *et al*. (2003), Iowa, USA, 1988–89	Colon	685 cases identified from Iowa Cancer Registry, aged 40–85 years; white only; 86% deceased or too ill with proxy respondents; cases confirmed by histology (348) or positive cytology (28); response rate, 88%	2434 population-based selected from driver's licence records (aged <65 years) or from Health Care Finance Administration listing (aged > 65 years); matched by age, sex; response rates, 82% (aged < 65) and 80% (aged > 65)	Postal questionnaire; lifetime residential water source history; 55-item food-frequency questionnaire assessed nitrate, nitrite, vitamin C; nitrate monitoring data from 1960–87 from public utilities in Iowa; imputation of values for years without nitrate data; drinking-water analyses: 376 colon cases, 338 rectal cases, 1244 controls with ≥ 70% person–years 1960 onward with nitrate estimates	**Average nitrate (mg/L nitrate-N) in public supplies, 1960–89**			Age, gender	Significant interaction ($P < 0.10$) of water nitrate level with vitamin C, meat intake; odds ratio > 10 years nitrate at levels > 5 m/L nitrate-N and > median meat intake, 2.2 (1.4–3.6) versus 0 years > 5 mg/L nitrate-N and low meat intake; no significant for interaction for water nitrate with tobacco smoking, history of bowel inflammation, beverage consumption or high-fibre food intake
					≤ 1	172	1.0 (reference)		
					> 1–≤ 3	116	1.0 (0.8–1.3)		
					> 3–≤ 5	27	0.7 (0.4–1.1)		
					> 5	61	1.2 (0.8–1.7)		
					Years with nitrate >5 mg/L nitrate-N				
					0	240	1.0 (reference)		
					1–≤ 10	65	0.8 (0.6–1.1)		
					> 10	71	1.2 (0.9–1.6)		
					Vitamin C/years > 5 mg/L				
					High vit C/0 year	74	1.0 (reference)		
					Low vit C/0 years	97	1.4 (1.0–1.9)		
					High vit C/1–10 years	22	0.9 (0.5–1.5)		
					Low vit C/1–10 years	28	1.1 (0.7–1.9)		
					High vit C/> 10 years	24	1.1 (0.7–1.9)		
					Low vit C/> 10 years	35	2.0 (1.2–3.3)		

Table 2.12 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
De Roos *et al*. (2003) (contd)	Colon (contd)				**Dietary nitrate (mg/day)**				
					≤ 59.3	89	1.0 (reference)		
					59.4–86.86	68	0.8 (0.6–1.2)		
					86.7–122	68	0.8 (0.5–1.1)		
					> 22	55	0.7 (0.4–1.0)		
					Dietary nitrite (mg/day)				
					≤ 0.705	90	1.0 (reference)		
					0.706–0.94	73	1.1 (0.8–1.6)		
					0.94–1.26	48	0.9 (0.6–1.3)		
					> 1.26	69	1.5 (1.0–2.1)		
	Rectum	655 cases identified from Iowa Cancer Registry, aged 40–85 years; white only; 86% deceased or too ill with proxy respondents; cases confirmed by histology (348) or positive cytology (28); response rate, 88%			**Average nitrate (mg/L nitrate-N) in public supplies, 1960–89**			Age, gender, years with chlorinated surface water	No significant interaction with vitamin C, meat intake, tobacco smoking, history of bowel inflammation, beverage consumption or high-fibre food intake
					≤ 1	154	1.0 (reference)		
					> 1–≤ 3	98	0.8 (0.6–1.1)		
					> 3–≤ 5	30	0.7 (0.5–1.2)		
					> 5	56	1.2 (0.8–1.8)		
					Years with nitrate >5 mg/L nitrate-N				
					0	222	1.0 (reference)		
					1–≤ 10	57	0.8 (0.6–1.1)		
					> 10	59	1.1 (0.7–1.5)		

Table 2.12 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
De Roos *et al*. (2003) (contd)	Rectum (contd)				**Vitamin C/years**				
					> 5 mg/L				
					High vit C/0 year	87	1.0 (reference)		
					Low vit C/0 years	82	0.9 (0.7–1.3)		
					High vit C/1–10 years	15	0.5 (0.3–1.0)		
					Low vit C/1–10 years	24	0.8 (0.5–1.3)		
					High vit C/> 10 years	18	0.7 (0.4–1.3)		
					Low vit C/> 10 years	23	1.1 (0.6–1.8)		
					Dietary nitrate (mg/day)				
					≤ 59.3	56	1.0 (reference)		
					59.4–86.8	67	1.3 (0.9–1.9)		
					86.7–122	66	1.2 (0.8–1.8)		
					> 122	60	1.1 (0.8–1.7)		
					Dietary nitrite (mg/day)				
					≤ 0.705	74	1.0 (reference)		
					0.706–0.94	62	1.1 (0.7–1.6)		
					0.94–1.26	43	0.9 (0.6–1.4)		
					> 1.26	70	1.7 (1.1–2.5)		

CI, confidence interval; vit C, vitamin C

associated with a significant, 2.1-fold increase in risk. In the case–control study (De Roos *et al*., 2003), the highest quartile of dietary intake of nitrite was associated with an increased risk for colon cancer (odds ratio for the highest versus lowest quartile, 1.5; 95% CI, 1.0–2.1) and rectal cancer (odds ratio for the highest versus lowest quartile, 1.7; 95% CI, 1.1–2.5).

Meta-analyses of epidemiological studies that evaluated consumption of meat and the occurrence of colorectal cancer (Sandhu *et al*., 2001; Norat *et al*., 2002) reported significantly increased risks for the consumption of red meats and cured meats such as frankfurters, bacon, ham and luncheon meat. Although most cured meats are usually treated with nitrite, few studies estimated dietary intake of nitrite directly.

2.10 Pancreatic cancer

2.10.1 *Ingested nitrate*

One cohort study (Weyer *et al*., 2001) and one case–control study (Coss *et al*., 2004) evaluated nitrate in both the drinking-water and diet and risk for pancreatic cancer. Two additional case–control studies (Howe *et al*., 1990; Baghurst *et al*., 1991) evaluated dietary intake of nitrate alone.

A cohort study of women in Iowa, USA (Weyer *et al*., 2001; described in detail in Section 4.1), found no significant association with the long-term average levels of nitrate in public water supplies that served the current residence and the incidence of pancreatic cancer (Table 2.10); neither were quartiles of dietary intake of nitrate associated with risk.

A population-based case–control study in Canada of 249 cases and 505 controls (Howe *et al*., 1990) evaluated the risk for pancreatic cancer in relation to dietary intakes of nitrate using a food-frequency questionnaire and a database of nitrate values obtained from the published literature (Table 2.13). Modelled as a continuous variable and adjusting for age, sex, tobacco smoking and intake of fibre and calories, no significant association was observed between intake of nitrate and risk for pancreatic cancer.

Baghurst *et al*. (1991) conducted a population-based case–control study of pancreatic cancer in Australia among 104 cases and 253 controls (Table 2.13). Dietary intake of nitrate was estimated from a food-frequency questionnaire with nitrate values provided by Howe *et al*. (1990). Increasing quartiles of dietary intake of nitrate were associated with decreasing risk (odds ratio for highest versus lowest quartile, 0.45; 95% CI, 0.22–0.94) after adjustment for total energy, tobacco smoking and alcohol consumption.

A population-based case–control study (Coss *et al*., 2004) in Iowa, USA, included 376 cases of pancreatic cancer and 2034 controls. The analyses of drinking-water were limited to persons who had spent 70% of their person–years from 1960 onwards in an area with an estimate of levels of nitrate in the public water supply (189 cases, 1244 controls). The average level of nitrate in public water supplies (1960–87) and the number of years that the person used supplies with > 10 and > 7.5 mg/L nitrate-N were evaluated. No association was observed between any of the metrics of nitrate in the

Table 2.13. Case–control studies of nitrate in the drinking-water and nitrate and nitrite in the diet and pancreatic cancer

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Howe *et al.* (1990), metropolitan Toronto, Canada, 1983–86	Pancreas	249 diagnosed in 20 Toronto hospitals, aged 35–79 years, resident in greater metropolitan Toronto; 69% histologically confirmed, remainder clinically or radiologically; 194 interviews with proxies (62% spouse, 31% child); response rate, 46%	505 population-based selected from population rolls; matched by age, sex, residence in Toronto area; 194 interviews with proxies of selected controls (72% spouse; 19% child); response rate, 31%	Interview administered 200-item FFQ validated for the study population	Dietary nitrate, mean daily difference Q4 versus Q1: 35.1 mg *P* for trend Dietary nitrite, mean daily difference Q4 versus Q1: 1.6 mg *P* for trend		1.21 (0.72–2.02) 0.48 0.64 (0.34–1.22) 0.17	Age, sex, respondent status, total calories, fibre, cigarettes/day	Odds ratios estimated from continuous variable models; interaction with vitamin C not evaluated

Table 2.13 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Baghurst *et al.* (1991), Adelaide, South Australia, 1984–87	Pancreas	104 (52 men, 52 women) from South Australian Cancer Registry; only 16 cases had next-of-kin respondents due to rapid enrolment; response rates for case series which included pancreas, gall-bladder and bile ducts was 62% for men and 63% for women	253 population-based from electoral rolls; matched on age, sex; response rates, 57% for men and 51% for women	Self-administered 179-item FFQ; validated for the study population; nitrate, nitrite, nitrosamine values from Howe *et al.* (1990; Canada) with local data for alcohol and cured meats from producers in Australia	**Dietary nitrate (mg/day)** Q1 Q2 Q3 Q4 *P* for trend **Dietary nitrite (mg/day)** Q1 Q2 Q3 Q4 *P* for trend		 1.0 (reference) 0.90 (0.46–1.77) 0.73 (0.36–1.48) 0.45 (0.22–0.94) 0.027 1.0 (reference) 1.01 (0.51–1.99) 0.65 (0.32–1.30) 0.92 (0.46–1.84) 0.49	Total energy, alcohol, tobacco	Interaction with vitamin C or animal sources separately not evaluated; nitrosamines associated with non-significantly increased risk (*P* for trend = 0.11); [histological confirmation not mentioned]

Table 2.13 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Coss *et al.* (2004), Iowa, USA, 1985–87	Pancreas	376 (202 white men, 174 white women) identified from Iowa Cancer Registry, aged 40–85 years; 86% deceased or too ill with proxy respondents; cases confirmed by histology (348) or positive cytology (28); response rate, 88%	2034 population-based selected from driver's licence records (aged < 65) or from Health Care Finance Administration listing (aged > 65); matched by age, sex; response rates, 82% (aged < 65) and 80% (aged > 65)	Postal questionnaire; lifetime residential water source history; 55-item FFQ; monitoring data for 1960–87 from public utilities in Iowa; imputed values for years without data; drinking water nitrate analyses: 189 cases, 1244 controls with ≥ 70% person–years 1960 onward with nitrate estimates	**Average nitrate (mg/L nitrate-N) in public supplies, 1960–87**			Age, gender, cigarette use	No significant associations with years using a public supply with ≥ 7.5 or 10 mg/L nitrate-N; no interaction with smoking or vitamin C intake [data not shown]; association not significant after excluding proxies who were not spouses; no association for plant sources of nitrite among men or women [data not shown]
					< 0.6	50	1.0 (reference)		
					0.6–< 1.3	62	1.2 (0.79–1.8)		
					1.3–2.8	28	0.54 (0.33–0.89)		
					> 2.8	49	0.99 (0.64–1.5)		
					Dietary nitrate (mg/day)			Age, cigarette use, total calories	
					Men				
					< 58	26	1.0 (reference)		
					58–82	33	1.1 (0.63–1.9)		
					83–117	39	1.2 (0.70–2.0)		
					> 117	43	1.0 (0.60–1.8)		
					Women				
					< 63	39	1.0 (reference)		
					63–90	33	0.99 (0.58–1.7)		
					91–126	24	0.64 (0.36–1.1)		
					> 126	26	0.53 (0.29–0.97)		

Table 2.13 (contd)

Reference, study location, period	Organ site	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Coss *et al.* (2004) (contd)					**Dietary nitrite (mg/day)**				
					Men				
					< 0.75	15	1.0 (reference)		
					0.75–0.98	22	1.0 (0.52–2.0)		
					0.99–1.30	40	1.5 (0.81–2.9)		
					> 1.30	64	1.5 (0.79–3.0)		
					Women				
					< 0.56	18	1.0 (reference)		
					0.56–0.71	32	1.8 (0.94–3.4)		
					0.72–0.93	32	1.4 (0.72–2.6)		
					> 0.93	40	1.3 (0.65–2.5)		
					Dietary nitrite from animal sources (mg/day)				
					Men				
					< 0.22	9	1.0 (reference)		
					0.22–0.31	22	2.1 (0.95–4.8)		
					0.32–0.53	60	3.8 (1.8–8.0)		
					> 0.53	50	2.3 (1.1–5.1)		
					Women				
					< 0.13	13	1.0 (reference)		
					0.13–0.18	32	2.4 (1.3–4.7)		
					0.19–0.26	26	1.9 (0.94–4.0)		
					> 0.26	51	3.2 (1.6–6.4)		

CI, confidence interval, FFQ, food-frequency questionnaire; Q, quartile

drinking-water and risk for pancreatic cancer. No evidence of an interaction between the levels of nitrate in water and intake of vitamin C or tobacco smoking was found [results of analyses of interaction were not presented]. Increasing quartiles of dietary intake of nitrate were inversely associated with risk in women (odds ratio for the highest versus lowest quartile, 0.53; 95% CI, 0.29–0.97) but not in men (odds ratio, 1.0; 95% CI, 0.6–1.8). When analyses were limited to self-responding women and proxies who were husbands of the subjects, no significant association with risk was observed.

2.10.2 *Ingested nitrite*

The three case–control studies that evaluated dietary intake of nitrate also estimated dietary intake of nitrite using the same methods (Table 2.13).

Howe *et al*. (1990) modelled intake of nitrite as a continuous variable and found no association with the risk for pancreatic cancer. Baghurst *et al*. (1991) evaluated increasing quartiles of dietary intake of nitrite and found no association with the risk for pancreatic cancer; however, increasing quartiles of dietary intake of nitrosamines were associated with a non-significant positive trend in risk (P for trend = 0.11).

In the case–control study in Iowa (Coss *et al*., 2004), a slight elevated risk for pancreatic cancer was observed for the high quartile of consumption of dietary nitrite (odds ratio for men, 1.5; odds ratio for women, 1.3). When animal sources of nitrite were evaluated separately, risks were higher (odds ratio for highest versus lowest quartile: men, 2.3; women, 3.2) and were statistically significant.

2.11 Lung

2.11.1 *Ingested nitrate*

One cohort study (Weyer *et al*., 2001) (described in detail in Section 2.4) evaluated nitrate in the drinking-water and the diet and the risk for lung cancer among 252 cases. No significant relationship between average levels of nitrate (median, 1.0 mg/L nitrogen-N; interquartile range, 0.36–2.46 mg/L) in public water supplies and the risk for lung cancer was observed. Quartiles of dietary nitrate were not significantly associated with risk (odds ratio for highest versus lowest quartile, 0.78; 95% CI, 0.55–1.11).

One case–control study (Goodman *et al*., 1992) evaluated dietary intake of nitrate and the risk for lung cancer and reported an inverse association [results not presented in the paper; 86% of intake was reported to be from vegetables].

2.11.2 *Ingested nitrite*

A population-based case–control study in Oahu, Hawaii, USA, of 326 cases and 865 controls (Goodman *et al*., 1992) found elevated risks for lung cancer with increasing quartiles of dietary intake of nitrite among men and women (Table 2.11) with a significant positive trend among men (P for trend = 0.02). Risk estimates were adjusted

for ethnicity, tobacco smoking, and intake of β-carotene. Intake of nitrite was primarily from consumption of cured meat. The authors did not evaluate interactions with nitrite and vitamin C or other factors that affect endogenous nitrosation. The association with intake of individual cured meats was stronger among current smokers than among former smokers, and was somewhat stronger for squamous-cell carcinoma than for adenocarcinoma. Levels of NDMA were also estimated in this study and showed a stronger association with risk than nitrite among both men (P for trend < 0.001) and women (P for trend = 0.04).

2.12 Liver

No cohort or case–control studies have evaluated ingested nitrate and nitrite in relation to liver cancer.

Ecological studies

The study by Wu *et al*. (1993) in 69 counties of China (described in detail in Section 2.2.1) found a statistically significant positive correlation between mortality rates for liver cancer (ages 0–64 years in 1973–75) and urinary concentrations of nitrate ($r = 0.25$; $P < 0.05$). Mortality from these cancers was not significantly correlated with nitrosation potential, NPRO or specific *N*-nitroso amino acids.

An ecological study of cholangiocarcinoma in Thailand (Srianujata *et al*., 1984) evaluated salivary and urinary concentrations of nitrate and nitrite in men and women in low- (12 subjects) and high-risk (32 subjects) areas who consumed regular meals. Multiple samples were taken within 2 h after eating. Levels of nitrate and nitrite in saliva were significantly higher (two to five fold) among those living in high-risk areas. Urinary levels of nitrate were higher at some time points, but all levels of nitrite were similar. Mitacek *et al*. (1999) measured the levels of volatile nitrosamines, nitrate and nitrite in foods typically consumed in high- and low-risk areas for liver cancer in Thailand. Concentrations of nitrate and nitrite were not correlated with volatile nitrosamines. Specific volatile nitrosamines tended to be found at higher concentrations in foods that were consumed in the high-risk areas; however, no formal statistical analyses were conducted.

2.13 References

Ahlbom A, Navier IL, Norell S *et al*. (1986). Nonoccupational risk indicators for astrocytomas in adults. *Am J Epidemiol*, 124:334–337. PMID:3728449

Airoldi L, Galli A, Mercato F *et al*. (1997). Salivary nitrate, nitrite and N-nitroso compounds in patients with cancer of the upper aerodigestive tract. *Eur J Cancer Prev*, 6:351–356. doi:10.1097/00008469-199708000-00006. PMID:9370097

Al-Dabbagh S, Forman D, Bryson D *et al*. (1986). Mortality of nitrate fertiliser workers. *Br J Ind Med*, 43:507–515. PMID:3015194

Armijo R, Gonzalez A, Orellana M *et al*. (1981). Epidemiology of gastric cancer in Chile: II – Nitrate exposures and stomach cancer frequency. *Int J Epidemiol*, 10:57–62. doi:10.1093/ije/10.1.57. PMID:7239764

Badawi AF, Hosny G, el-Hadary M, Mostafa MH (1998). Salivary nitrate, nitrite and nitrate reductase activity in relation to risk of oral cancer in Egypt. *Dis Markers*, 14:91–97. PMID:9868596

Baghurst PA, McMichael AJ, Slavotinek AH *et al*. (1991). A case–control study of diet and cancer of the pancreas. *Am J Epidemiol*, 134:167–179. PMID:1862800

Barbone F, Austin H, Partridge EE (1993). Diet and endometrial cancer: a case–control study. *Am J Epidemiol*, 137:393–403. PMID:8460621

Barrett JH, Parslow RC, McKinney PA *et al*. (1998). Nitrate in drinking water and the incidence of gastric, esophageal, and brain cancer in Yorkshire, England. *Cancer Causes Control*, 9:153–159. doi:10.1023/A:1008878126535. PMID:9578292

Bartsch H, Ohshima H, Pignatelli B, Calmels S (1992). Endogenously formed N-nitroso compounds and nitrosating agents in human cancer etiology. *Pharmacogenetics*, 2:272–277. doi:10.1097/00008571-199212000-00005. PMID:1339085

Beresford SA (1985). Is nitrate in the drinking water associated with the risk of cancer in the urban UK? *Int J Epidemiol*, 14:57–63. doi:10.1093/ije/14.1.57. PMID:3988441

Blowers L, Preston-Martin S, Mack WJ (1997). Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). *Cancer Causes Control*, 8:5–12. doi:10.1023/A:1018437031987. PMID:9051317

Boeing H, Frentzel-Beyme R, Berger M *et al*. (1991). Case–control study on stomach cancer in Germany. *Int J Cancer*, 47:858–864. doi:10.1002/ijc.2910470612. PMID:2010228

Boeing H, Schlehofer B, Blettner M, Wahrendorf J (1993). Dietary carcinogens and the risk for glioma and meningioma in Germany. *Int J Cancer*, 53:561–565. doi:10.1002/ijc.2910530406. PMID:8436429

Bos PM, Van den Brandt PA, Wedel M, Ockhuizen T (1988). The reproducibility of the conversion of nitrate to nitrite in human saliva after a nitrate load. *Food Chem Toxicol*, 26:93–97. doi:10.1016/0278-6915(88)90104-4. PMID:3366416

Buiatti E, Palli D, Decarli A *et al*. (1990). A case–control study of gastric cancer and diet in Italy: II. Association with nutrients. *Int J Cancer*, 45:896–901. doi:10.1002/ijc.2910450520. PMID:2335393

Bunin GR (1994) Letter to the editor: cured meats and childhood cancer. *Cancer Causes Control*, **5**, 485–486.

Bunin GR, Kuijten RR, Buckley JD *et al*. (1993). Relation between maternal diet and subsequent primitive neuroectodermal brain tumors in young children. *New Engl J Med*, 329:536–541. doi:10.1056/NEJM199308193290804. PMID:8336753

Bunin GR, Kuijten RR, Boesel CP *et al*. (1994). Maternal diet and risk of astrocytic glioma in children: a report from the Childrens Cancer Group (United States and Canada). *Cancer Causes Control*, 5:177–187. doi:10.1007/BF01830264. PMID:8167265

Bunin GR, Kushi LH, Gallagher PR *et al*. (2005). Maternal diet during pregnancy and its association with medulloblastoma in children: a Children's Oncology Group study (United States). *Cancer Causes Control*, 16:877–891. PMID:16132798 doi:10.1007/s10552-005-3144-7

Burch JD, Craib KJ, Choi BC *et al*. (1987). An exploratory case–control study of brain tumors in adults. *J Natl Cancer Inst*, 78:601–609. PMID:3104645

Cantor KP (1997). Drinking water and cancer. *Cancer Causes Control*, 8:292–308. doi:10.1023/A:1018444902486. PMID:9498894

Chen VW, Abu-Elyazeed RR, Zavala DE *et al*. (1990). Risk factors of gastric precancerous lesions in a high-risk Colombian population. II. Nitrate and nitrite. *Nutr Cancer*, 13:67–72. doi:10.1080/01635589009514046. PMID:2300495

Chen H, Ward MH, Tucker KL *et al*. (2002). Diet and risk of adult glioma in eastern Nebraska, United States. *Cancer Causes Control*, 13:647–655. doi:10.1023/A:1019527225197. PMID:12296512

Cocco P, Broccia G, Aru G *et al*. (2003). Nitrate in community water supplies and incidence of non-Hodgkin's lymphoma in Sardinia, Italy. *J Epidemiol Community Health*, 57:510–511. doi:10.1136/jech.57.7.510. PMID:12821696

Cordier S, Iglesias MJ, Le Goaster C *et al*. (1994). Incidence and risk factors for childhood brain tumors in the Ile de France. *Int J Cancer*, 59:776–782. doi:10.1002/ijc.2910590612. PMID:7989118

Correa P, Haenszel W, Cuello C *et al*. (1990a). Gastric precancerous process in a high risk population: cross-sectional studies. *Cancer Res*, 50:4731–4736. PMID:2369747

Correa P, Haenszel W, Cuello C *et al*. (1990b). Gastric precancerous process in a high risk population: cohort follow-up. *Cancer Res*, 50:4737–4740. PMID:2369748

Coss A, Cantor KP, Reif JS *et al*. (2004). Pancreatic cancer and drinking water and dietary sources of nitrate and nitrite. *Am J Epidemiol*, 159:693–701. doi:10.1093/aje/kwh081. PMID:15033647

Cuello C, Correa P, Haenzel W *et al*. (1976). Gastric cancer in Colombia. I. Cancer risk and suspect environmental agents. *J Natl Cancer Inst*, 57:1015–1020. PMID:1003537

Cuello C, López J, Correa P *et al*. (1979). Histopathology of gastric dysplasias: correlations with gastric juice chemistry. *Am J Surg Pathol*, 3:491–500. PMID:534386

Davies JM (1980). Stomach cancer mortality in Worksop and other Nottinghamshire mining towns. *Br J Cancer*, 41:438–445. PMID:7387834

De Roos AJ, Ward MH, Lynch CF, Cantor KP (2003). Nitrate in public water supplies and the risk of colon and rectum cancers. *Epidemiology*, 14:640–649. doi:10.1097/01.ede.0000091605.01334.d3. PMID:14569178

De Stefani E, Deneo-Pellegrini H, Carzoglio JC *et al*. (1996). Dietary nitrosodimethylamine and the risk of lung cancer: a case–control study from Uruguay. *Cancer Epidemiol Biomarkers Prev*, 5:679–682. PMID:8877057

Dich J, Järvinen R, Knekt P, Penttilä PL (1996). Dietary intakes of nitrate, nitrite and NDMA in the Finnish Mobile Clinic Health Examination Survey. *Food Addit Contam*, 13:541–552. PMID:8799716

Engel LS, Chow WH, Vaughan TL *et al*. (2003). Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst*, 95:1404–1413. PMID:13130116

Environmental Protection Agency (2003). *National Primary Drinking Water Standards* (EPA-816/F-03–016), Washington DC, Office of Water. Available at: www.epa.gov/safewater

Forman D, Al-Dabbagh S, Doll R (1985). Nitrates, nitrites and gastric cancer in Great Britain. *Nature*, 313:620–625. doi:10.1038/313620a0. PMID:3974695

Foster AM, Prentice AG, Copplestone JA *et al*. (1997). The distribution of leukaemia in association with domestic water quality in south west England. *Eur J Cancer Prev*, 6:11–19. doi:10.1097/00008469-199702000-00003. PMID:9161807

Fraser P, Chilvers C (1981). Health aspects of nitrate in drinking water. *Sci Total Environ*, 18:103–116. doi:10.1016/S0048-9697(81)80053-8. PMID:6262908

Freedman DM, Cantor KP, Ward MH, Helzlsouer KJ (2000). A case–control study of nitrate in drinking water and non-Hodgkin's lymphoma in Minnesota. *Arch Environ Health*, 55:326–329. doi:10.1080/00039890009604024. PMID:11063407

Geleperin A, Moses VJ, Fox G (1976). Nitrate in water supplies and cancer. *Ill Med J*, 149:251–253.

Giles GG, McNeil JJ, Donnan G *et al*. (1994). Dietary factors and the risk of glioma in adults: results of a case–control study in Melbourne, Australia. *Int J Cancer*, 59:357–362. doi:10.1002/ijc.2910590311. PMID:7927941

Gilli G, Corrao G, Favilli S (1984). Concentrations of nitrates in drinking water and incidence of gastric carcinomas: first descriptive study of the Piemonte Region, Italy. *Sci Total Environ*, 34:35–48. doi:10.1016/0048-9697(84)90039-1. PMID:6710137

González CA, Riboli E, Badosa J *et al*. (1994). Nutritional factors and gastric cancer in Spain. *Am J Epidemiol*, 139:466–473. PMID:8154470

Goodman MT, Hankin JH, Wilkens LR, Kolonel LN (1992). High-fat foods and the risk of lung cancer. *Epidemiology*, 3:288–299. doi:10.1097/00001648-199207000-00004. PMID:1637893

Gulis G, Czompolyova M, Cerhan JR (2002). An ecologic study of nitrate in municipal drinking water and cancer incidence in Trnava District, Slovakia. *Environ Res*, 88:182–187. doi:10.1006/enrs.2002.4331. PMID:12051796

Hansson LE, Nyrén O, Bergström R *et al*. (1994). Nutrients and gastric cancer risk. A population-based case–control study in Sweden. *Int J Cancer*, 57:638–644. doi:10.1002/ijc.2910570505. PMID:8194870

Hartman PE (1983). Review: putative mutagens and carcinogens in foods. I. Nitrate/nitrite ingestion and gastric cancer mortality. *Environ Mutag*, 5:111–121. doi:10.1002/em.2860050112. PMID:6832084

Hill MJ, Hawksworth G, Tattersall G (1973). Bacteria, nitrosamines and cancer of the stomach. *Br J Cancer*, 28:562–567. PMID:4593224

Hochberg F, Toniolo P, Cole P, Salcman M (1990). Nonoccupational risk indicators of glioblastoma in adults. *J Neurooncol*, 8:55–60. doi:10.1007/BF00182087. PMID:2319291

Howe GR, Burch JD, Chiarelli AM *et al*. (1989). An exploratory case–control study of brain tumors in children. *Cancer Res*, 49:4349–4352. PMID:2743324

Howe GR, Jain M, Miller AB (1990). Dietary factors and risk of pancreatic cancer: results of a Canadian population-based case–control study. *Int J Cancer*, 45:604–608. doi:10.1002/ijc.2910450405. PMID:2157670

Huncharek M, Kupelnick B (2004). A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology*, 23:78–84. doi:10.1159/000073979. PMID:14739572

Huncharek M, Kupelnick B, Wheeler L (2003). Dietary cured meat and the risk of adult glioma: a meta-analysis of nine observational studies. *J Environ Pathol Toxicol Oncol*, 22:129–137. doi:10.1615/JEnvPathToxOncol.v22.i2.60. PMID:14533876

IARC (2004). Some drinking-water disinfectants and contaminants, including arsenic. *IARC Monogr Eval Carcinog Risks Hum*, 84:1–477. PMID:15645577

Jensen OM (1982). Nitrate in drinking water and cancer in northern Jutland, Denmark, with special reference to stomach cancer. *Ecotoxicol Environ Saf*, 6:258–267. doi:10.1016/0147-6513(82)90016-1. PMID:7106030

Joossens JV, Hill MJ, Elliott P *et al*.; European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group (1996). Dietary salt, nitrate and stomach cancer mortality in 24 countries. *Int J Epidemiol*, 25:494–504. doi:10.1093/ije/25.3.494. PMID:8671549

Juhasz L, Hill MJ, Nagy G (1980). Possible relationship between nitrate in drinking water and incidence of stomach cancer. *IARC Sci Publ*, 97:619–623.

Kamiyama S, Ohshima H, Shimada A *et al*. (1987). Urinary excretion of *N*-nitrosamino acids and nitrate by inhabitants in high- and low-risk areas for stomach cancer in northern Japan. *IARC Sci Publ*, 84:497–502.

Kaplan S, Novikov I, Modan B (1997). Nutritional factors in the etiology of brain tumors: potential role of nitrosamines, fat, and cholesterol. *Am J Epidemiol*, 146:832–841. PMID:9384204

Knekt P, Järvinen R, Dich J, Hakulinen T (1999). Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. *Int J Cancer*, 80:852–856. doi:10.1002/(SICI)1097-0215(19990315)80:6<852::AID-IJC9>3.0.CO;2-S PMID:10074917

Knight TM, Forman D, Pirastu R *et al*. (1990). Nitrate and nitrite exposure in Italian populations with different gastric cancer rates. *Int J Epidemiol*, 19:510–515. doi:10.1093/ije/19.3.510. PMID:2262241

Knight T, Pirastu R, Palli D *et al*. (1992). Nitrate and N-nitrosoproline excretion in two Italian regions with contrasting rates of gastric cancer: the role of nitrate and other factors in endogenous nitrosation. *Int J Cancer*, 50:736–739. doi:10.1002/ijc.2910500512. PMID:1544707

Kuijten RR, Bunin GR, Nass CC, Meadows AT (1990). Gestational and familial risk factors for childhood astrocytoma: results of a case–control study. *Cancer Res*, 50:2608–2612. PMID:2328486

La Vecchia C, Ferraroni M, D'Avanzo B *et al*. (1994). Selected micronutrient intake and the risk of gastric cancer. *Cancer Epidemiol Biomarkers Prev*, 3:393–398. PMID:7920206

La Vecchia C, Negri E, Franceschi S, Decarli A (1997). Case–control study on influence of methionine, nitrite, and salt on gastric carcinogenesis in northern Italy. *Nutr Cancer*, 27:65–68 doi:10.1080/01635589709514503. PMID:8970184

Law G, Parslow R, McKinney P, Cartwright R (1999). Non-Hodgkin's lymphoma and nitrate in drinking water: A study in Yorkshire, United Kingdom. *J Epidemiol Community Health*, 53:383-384. doi:10.1136/jech.54.10.772a. PMID:10396486

Lee M, Wrensch M, Miike R (1997). Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay Area (California, USA). *Cancer Causes Control*, 8:13–24. doi:10.1023/A:1018470802969. PMID:9051318

Lin K, Shen W, Shen Z *et al*. (2003). Estimation of the potential for nitrosation and its inhibition in subjects from high- and low-risk areas for esophageal cancer in southern China. *Int J Cancer*, 107:891–895. doi:10.1002/ijc.11506. PMID:14601047

van Loon AJ, Botterweck AA, Goldbohm RA *et al*. (1997). Nitrate intake and gastric cancer risk: results from the Netherlands cohort study. *Cancer Lett*, 114:259–261. doi:10.1016/S0304-3835(97)04677-6. PMID:9103306

van Loon AJ, Botterweck AA, Goldbohm RA *et al*. (1998). Intake of nitrate and nitrite and the risk of gastric cancer: a prospective cohort study. *Br J Cancer*, 78:129–135. PMID:9662263

Lu SH, Ohshima H, Fu HM *et al*. (1986). Urinary excretion of N-nitrosamino acids and nitrate by inhabitants of high- and low-risk areas for esophageal cancer in Northern China: endogenous formation of nitrosoproline and its inhibition by vitamin C. *Cancer Res*, 46:1485–1491. PMID:3943105

Lubin F, Farbstein H, Chetrit A *et al*. (2000). The role of nutritional habits during gestation and child life in pediatric brain tumor etiology. *Int J Cancer*, 86:139–143. doi:10.1002/(SICI)1097-0215(20000401)86:1<139::AID-IJC22>3.0.CO;2-C. PMID:10728608

van Maanen JM, Dallinga JW, Kleinjans JC (1996). Environmental exposure to N-nitroso compounds and their precursors. *Eur J Cancer Prev*, 5 Suppl 1;29–31. doi:10.1097/00008469-199609001-00006. PMID:8972289

Mayne ST, Risch HA, Dubrow R *et al*. (2001). Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev*, 10:1055–1062. PMID:11588131

McCredie M, Maisonneuve P, Boyle P (1994a). Antenatal risk factors for malignant brain tumours in New South Wales children. *Int J Cancer*, 56:6–10. PMID:8262678

McCredie M, Maisonneuve P, Boyle P (1994b). Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. *Int J Cancer*, 56:11–15. PMID:8262665

Mills PK, Preston-Martin S, Annegers JF *et al*. (1989). Risk factors for tumors of the brain and cranial meninges in Seventh-Day Adventists. *Neuroepidemiology*, 8:266–275. doi:10.1159/000110193. PMID:2812186

Mitacek EJ, Brunnemann KD, Suttajit M *et al*. (1999). Exposure to N-nitroso compounds in a population of high liver cancer regions in Thailand: volatile nitrosamine (VNA) levels in Thai food. *Food Chem Toxicol*, 37:297–305. doi:10.1016/S0278-6915(99)00017-4. PMID:10418946

Møller H (1997). Work in agriculture, childhood residence, nitrate exposure, and testicular cancer risk: a case–control study in Denmark. *Cancer Epidemiol Biomarkers Prev*, 6:141–144. PMID:9037566

Morales-Suarez-Varela M, Llopis Gonzalez A, Tejerizo Perez ML, Ferrandiz Ferragud J (1993). Concentration of nitrates in drinking water and its relationship with bladder cancer. *J Environ Pathol Toxicol Oncol*, 12:229–236. PMID:8189380

Morales-Suárez-Varela MM, Llopis-Gonzalez A, Tejerizo-Perez ML (1995). Impact of nitrates in drinking water on cancer mortality in Valencia, Spain. *Eur J Epidemiol*, 11:15–21. doi:10.1007/BF01719941. PMID:7489769

Mueller BA, Newton K, Holly EA, Preston-Martin S (2001). Residential water source and the risk of childhood brain tumors. *Environ Health Perspect*, 109:551–556. doi:10.2307/3455026. PMID:11445506

Mueller BA, Nielsen SS, Preston-Martin S *et al*. (2004). Household water source and the risk of childhood brain tumours: results of the SEARCH International Brain Tumor Study. *Int J Epidemiol*, 33:1209–1216 doi:10.1093/ije/dyh215. PMID:15567873

Murphy RS, Sadler CJ, Blot WJ (1998). Trends in cured meat consumption in relation to childhood and adult brain cancer in the United States. *Food Control*, 9:299–305. doi:10.1016/S0956-7135(98)00020-6.

Norat T, Lukanova A, Ferrari P, Riboli E (2002). Meat consumption and colorectal cancer risk: dose–response meta-analysis of epidemiological studies. *Int J Cancer*, 98:241–256. doi:10.1002/ijc.10126. PMID:11857415

Ohshima H, Bartsch H (1981). Quantitative estimation of endogenous nitrosation in humans by monitoring N-nitrosoproline excreted in the urine. *Cancer Res*, 41:3658–3662. PMID:7260920

Palli D, Russo A, Decarli A (2001). Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy. *Cancer Causes Control*, 12:163–172. doi:10.1023/A:1008970310963. PMID:11246845

Pobel D, Riboli E, Cornée J *et al*. (1995). Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case–control study in Marseille, France. *Eur J Epidemiol*, 11:67–73. doi:10.1007/BF01719947. PMID:7489775

Pogoda JM, Preston-Martin S (2001a). Maternal cured meat consumption during pregnancy and risk of paediatric brain tumour in offspring: potentially harmful levels of intake. *Public Health Nutr*, 4:183–189 doi:10.1079/PHN200060. PMID:11299090

Pogoda JM, Preston-Martin S (2001b). Letter to the editor: maternal cured meat consumption during pregnancy and risk of paediatric brain tumour in offspring: potentially harmful levels of intake, authors' response. *Public Health Nutr*, 4:1304–1305.

Preston-Martin S, Mack W (1991). Gliomas and meningiomas in men in Los Angeles County: Investigation of exposures to *N*-nitroso compounds. *IARC Sci Publi*, 105:197–203.

Preston-Martin S, Yu MC, Benton B, Henderson BE (1982). N-Nitroso compounds and childhood brain tumors: a case–control study. *Cancer Res*, 42:5240–5245. PMID:7139628

Preston-Martin S, Yu MC, Henderson BE, Roberts C (1983). Risk factors for meningiomas in men in Los Angeles County. *J Natl Cancer Inst*, 70:863–866. PMID:6573530

Preston-Martin S, Mack W, Henderson BE (1989). Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res*, 49:6137–6143. PMID:2790826

Preston-Martin S, Pogoda JM, Mueller BA *et al*. (1996). Maternal consumption of cured meats and vitamins in relation to pediatric brain tumors. *Cancer Epidemiol Biomarkers Prev*, 5:599–605. PMID:8824361

Rademacher JJ, Young TB, Kanarek MS (1992). Gastric cancer mortality and nitrate levels in Wisconsin drinking water. *Arch Environ Health*, 47:292–294. PMID:1497383

Risch HA, Jain M, Choi NW *et al*. (1985). Dietary factors and the incidence of cancer of the stomach. *Am J Epidemiol*, 122:947–959. PMID:2998182

Rogers MA, Vaughan TL, Davis S, Thomas DB (1995). Consumption of nitrate, nitrite, and nitrosodimethylamine and the risk of upper aerodigestive tract cancer. *Cancer Epidemiol Biomarkers Prev*, 4:29–36. PMID:7894321

Sandhu MS, White IR, McPherson K (2001). Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev*, 10:439–446. PMID:11352852

Sandor J, Kiss I, Farkas O, Ember I (2001). Association between gastric cancer mortality and nitrate content of drinking water: ecological study on small area inequalities. *Eur J Epidemiol*, 17:443–447. doi:10.1023/A:1013765016742. PMID:11855578

Sanz Anquela JM, Muñoz González ML, Ruiz Liso JM *et al*. (1989). [Correlation of the risk of gastric cancer in the province of Soria and the nitrate content of drinking water]. *Rev Esp Enferm Apar Dig*, 75:561–565 (in Spanish). PMID:2762637

Sarasua S, Savitz DA (1994). Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States). *Cancer Causes Control*, 5:141–148. doi:10.1007/BF01830260. PMID:8167261

Schwartzbaum JA, Fisher JL, Goodman J *et al*. (1999). Hypotheses concerning roles of dietary energy, cured meat, and serum tocopherols in adult glioma development. *Neuroepidemiology*, 18:156–166. doi:10.1159/000026207. PMID:10202269

Schymura MJ, Zheng D, Baptiste MS, Nasca PC (1996). A case–control study of childhood brain tumors and maternal lifestyle. *Am J Epidemiol*, 143:58.

Sierra R, Chinnock A, Ohshima H *et al*. (1993). In vivo nitrosoproline formation and other risk factors in Costa Rican children from high- and low-risk areas for gastric cancer. *Cancer Epidemiol Biomarkers Prev*, 2:563–568. PMID:8268774

Srianujata S, Tangbanleukal L, Bunyaratvej S, Valyasevi A (1984). Nitrate and nitrite in saliva and urine of inhabitants of areas of low and high incidence of cholangiocarcinoma in Thailand. *IARC Sci Publ*, 57:921–927.

Steindorf K, Schlehofer B, Becher H *et al*. (1994). Nitrate in drinking water. A case–control study on primary brain tumours with an embedded drinking water survey in Germany. *Int J Epidemiol*, 23:451–457. doi:10.1093/ije/23.3.451. PMID:7960368

Tsugane S, Tsuda M, Gey F, Watanabe S (1992). Cross-sectional study with multiple measurements of biological markers for assessing stomach cancer risks at the population level. *Environ Health Perspect*, 98:207–210. doi:10.2307/3431272. PMID:1486851

Van Leeuwen JA, Waltner-Toews D, Abernathy T *et al*. (1999). Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987–1991. *Int J Epidemiol*, 28:836–840. doi:10.1093/ije/28.5.836. PMID:10597979

Volkmer BG, Ernst B, Simon J *et al*. (2005). Influence of nitrate levels in drinking water on urological malignancies: a community-based cohort study. *Br J Urol Int*, 95:972–976. doi:10.1111/j.1464-410X.2005.05450.x. PMID:15839916

Wang YL, Lu SX, Li MX (1979). [Determination of nitrates and nitrites in well water from Yaocun commune, Linxien County, Henan province (author's transl)]. *Zhonghua Zhong Liu Za Zhi*, 1:201–205 (in Chinese). PMID:553796

Ward MH, Mark SD, Cantor KP *et al*. (1996). Drinking water nitrate and the risk of non-Hodgkin's lymphoma. *Epidemiology*, 7:465–471. doi:10.1097/00001648-199609000-00002. PMID:8862975

Ward MH, Pan WH, Cheng YJ *et al*. (2000). Dietary exposure to nitrite and nitrosamines and risk of nasopharyngeal carcinoma in Taiwan. *Int J Cancer*, 86:603–609. doi:10.1002/(SICI)1097-0215(20000601)86:5<603::AID-IJC1>3.0.CO;2-H. PMID:10797279

Ward MH, Cantor KP, Riley D *et al*. (2003). Nitrate in public water supplies and risk of bladder cancer. *Epidemiology*, 14:183–190. doi:10.1097/00001648-200303000-00012. PMID:12606884

Ward MH, Heineman EF, McComb RD, Weisenburger DD (2005). Drinking water and dietary sources of nitrate and nitrite and risk of glioma. *J Occup Environ Med*, 47:1260–1267. doi:10.1097/01.jom.0000184879.67736.ae. PMID:16340707

Ward MH, Cerhan JR, Colt JS, Hartge P (2006). Risk of non-Hodgkin lymphoma and nitrate and nitrite from drinking water and diet. *Epidemiology*, 17:375–382. doi:10.1097/01.ede.0000219675.79395.9f. PMID:16699473

Weisenberg E, Grauer F, Baron Y, Rajstein J (1982). An assessment of the implication of nitrate-rich water on salivary nitrate. *Ecotoxicol Environ Saf*, 6:97–101. doi:10.1016/0147-6513(82)90084-7. PMID:7067656

Weisenburger DD, Schmidt H, Steele SJ *et al*. (1987). Environmental epidemiology of non-Hodgkin's lymphoma (NHL) in eastern Nebraska. *Lab Invest*, 56:85A.

Weyer PJ, Cerhan JR, Kross BC *et al*. (2001). Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study. *Epidemiology*, 12:327–338. doi:10.1097/00001648-200105000-00013. PMID:11338313

Wilkens LR, Kadir MM, Kolonel LN *et al*. (1996). Risk factors for lower urinary tract cancer: the role of total fluid consumption, nitrites and nitrosamines, and selected foods. *Cancer Epidemiol Biomarkers Prev*, 5:161–166. PMID:8833615

WHO (2004) *Guidelines for Drinking-water Quality*, 3rd Ed., Vol. 1, *Recommendations*, Geneva, pp. 417–420.

Wu Y, Chen J, Ohshima H *et al*. (1993). Geographic association between urinary excretion of N-nitroso compounds and oesophageal cancer mortality in China. *Int J Cancer*, 54:713–719. doi:10.1002/ijc.2910540502. PMID:8325701

Yang CY, Cheng MF, Tsai SS, Hsieh YL (1998). Calcium, magnesium, and nitrate in drinking water and gastric cancer mortality. *Jpn J Cancer Res*, 89:124–130. PMID:9548438

Yi Z, Ohshima H, Bouvier G *et al*. (1993). Urinary excretion of nitrosamino acids and nitrate by inhabitants of high- and low-risk areas for nasopharyngeal carcinoma in southern China. *Cancer Epidemiol Biomarkers Prev*, 2:195–200. PMID:8318871

You WC, Zhang L, Yang CS *et al*. (1996). Nitrite, N-nitroso compounds, and other analytes in physiological fluids in relation to precancerous gastric lesions. *Cancer Epidemiol Biomarkers Prev*, 5:47–52. PMID:8770466

Zaldivar R (1977). Epidemiology of gastric and colo-rectal cancer in the United States and Chile with particular reference to the role of dietary and nutritional variables, nitrate fertilizer pollution, and N-nitroso compounds. *Zentralbl Bakteriol Orig B.*, 164:193–217.

Zaldívar R, Wetterstrand WH (1978). Nitrate nitrogen levels in drinking water of urban areas with high- and low-risk populations for stomach cancer: an environmental epidemiology study. *Z Krebsforsch Klin Onkol Cancer Res Clin Oncol*, 92:227–234. PMID:153065 doi:10.1007/BF00461645

Zatonski W, Ohshima H, Przewozniak K *et al*. (1989). Urinary excretion of N-nitrosamino acids and nitrate by inhabitants of high- and low-risk areas for stomach cancer in Poland. *Int J Cancer*, 44:823–827. doi:10.1002/ijc.2910440513. PMID:2583863

Zemła B, Kołosza Z (1979). [Nitrogen compounds (NH3, NO2, NO3) in drinking water and incidence of stomach cancer in population groups differentiated according to sex and place of birth]. *Pol Tyg Lek*, 34:1577–1580 (in Polish). PMID:514862

Zhang RF, Sun HL, Jin ML, Li SN (1984). A comprehensive survey of etiologic factors of stomach cancer in China. *Chin Med J*, 97:322–332. PMID:6439482

Zhang XL, Bing Z, Xing Z *et al*. (2003). Research and control of well water pollution in high esophageal cancer areas. *World J Gastroenterol*, 9:1187–1190. PMID:12800221