Environmental Contaminants as Etiologic Factors for Diabetes

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For both type 1 and type 2 diabetes mellitus, the rates have been increasing in the United States and elsewhere; rates vary widely by country, and genetic factors account for less than half of new cases. These observations suggest environmental factors cause both type 1 and type 2 diabetes. Occupational exposures have been associated with increased risk of diabetes. In addition, recent data suggest that toxic substances in the environment, other than infectious agents or exposures that stimulate an immune response, are associated with the occurrence of these diseases. We reviewed the epidemiologic data that addressed whether environmental contaminants might cause type 1 or type 2 diabetes. For type 1 diabetes, higher intake of nitrates, nitrites, and *N*-nitroso compounds, as well as higher serum levels of polychlorinated biphenyls have been associated with increased risk. Overall, however, the data were limited or inconsistent. With respect to type 2 diabetes, data on arsenic and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin relative to risk were suggestive of a direct association but were inconclusive. The occupational data suggested that more data on exposure to *N*-nitroso compounds, arsenic, dioxins, talc, and straight oil machining fluids in relation to diabetes would be useful. Although environmental factors other than contaminants may account for the majority of type 1 and type 2 diabetes, the etiologic role of several contaminants and occupational exposures deserves further study. *Key words*: arsenic, diabetes mellitus, epidemiology, nitrates, nitrites, nitroso compounds, occupations, polychlorinated biphenyls, tetrachlorodibenzodioxin. — *Environ Health Perspect* 109(suppl 6):871–876 (2001).
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Our charge was to assess whether monitoring of diabetes rates could be used as a method for detecting community exposure to critical pollutants. This question arose from the observation that the frequency of hospital admissions for diabetes varied substantially among several areas (Areas of Concern) on the border of the United States and Canada (*1*). The possibility that a corresponding distribution of toxic substances might account for the variation was suggested by scientists at the International Joint Commission, who advise the two governments on the Great Lakes Water Quality Agreement (*2*). We responded to their charge by reviewing data on whether environmental factors might be responsible for variation in rates of diabetes.

The notion that environmental contaminants could increase risk of diabetes is fairly new (*3–5*). That occupational exposure could increase risk, however, has been recognized since the 1970s, when an association with carbon disulfide was reported (*6*). Here we review the relevant epidemiologic data, which can be categorized as follows: type 1 diabetes in relation to nitrates, nitrites, and nitrosamines, and in relation to polychlorinated biphenyls (PCBs); and type 2 diabetes in relation to arsenic, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), and occupational exposures. We included occupational exposures in our review because they could affect local disease rates if the area around the industry were polluted or if a large proportion of the work force in a given area were employed by one industry. We begin with a brief description of the main types of diabetes and their epidemiology.

Type 1 diabetes results from decreased insulin production by the pancreatic β cells. β-cell deficiency is due to autoimmune processes, or, in some cases, to idiopathic destruction (*7*). The autoimmune process against β cells is thought to be triggered by a combination of genetic predisposition and environmental factors. The concordance of type 1 diabetes among monozygotic twins is 20–35% (*8,9*), suggesting that environmental factors play a large role in the etiology. The environmental factors usually considered etiologically relevant are infectious agents or dietary factors that stimulate an immune response (*10*). Poisonings with the rodenticide Vacor (Rohm and Haas Co., Philadelphia, PA), however, have caused type 1 diabetes (*11*). Furthermore, certain drugs, such as pentamidine, can be toxic to β cells (*12*). Agents that cause type 1 diabetes in animal models act through a variety of mechanisms (*13*), though all rely on toxins fairly specific for pancreatic β cells, such as alloxan and streptozotocin. Vacor, alloxan, and streptozotocin all include a urea structure; streptozotocin is also an *N*-nitroso compound.

The onset of type 1 diabetes is typically before adulthood. The incidence in whites is greater than in blacks or Asians (*14*). The incidence of type 1 diabetes has been increasing worldwide for approximately 40 years, with an average yearly increase in incidence of 3% (*15*). A typical incidence rate is $10/10^5$ person-years (world population standard), though rates vary markedly and are much higher in selected developed countries. Clustering of cases of type 1 diabetes, diagnosed among children who were together during a defined period, further supports an environmental component to the etiology (*16–18*). These cluster studies, however, offer little that allows one to distinguish the effect of contaminants from those of infectious agents or exposures that stimulate an immune response.

Type 2 diabetes is due to resistance to insulin action and a relative deficiency of insulin. Age, obesity, central adiposity, lack of physical activity, and dietary glycemic load are the main factors identified as responsible for the disease (*19*). The concordance rate among monozygous twins is about 30% (*9*). Whether chemical agents can cause type 2 diabetes in humans is not as clearly established as for type 1 diabetes, though suggestive data exist (*6*). Many drugs, however, exacerbate type 2 diabetes (*20*). As with type 1 diabetes, animal models of type 2 diabetes rely on a variety of mechanisms, and many include an element of impaired insulin action (*21*).

The onset of type 2 diabetes is typically during adulthood. Disease is more frequent among blacks, Mexican–Americans, and Native Americans (*14*). The prevalence of diabetes of all types was 6.5% in the United States in 1998 (*22*), with approximately 90–95% of cases due to type 2 diabetes (*23*). The prevalence of type 2 diabetes in the United States has increased by 33% during the past decade (*22,23*). This increase has been attributed to the rise in the prevalence of obesity (*22*). Worldwide the prevalence of type 2 diabetes varies roughly 10-fold, and the number of people with diabetes has increased 11% in the past 5 years (*24*).

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Regardless of type, patients with diabetes mellitus are at increased risk of small and large blood vessel disease and hyperlipidemia, resulting in retinopathy, neuropathy, vascular diseases such as myocardial infarction, stroke, aneurysm, and kidney failure, and they are also at increased risk of depression (*25*). The cost of diabetes in the United States in 1992 was estimated at $90 billion (*26*).

For both type 1 and type 2 diabetes, genetic factors by themselves appear to account for less than half of the disease; incidence rates have increased over relatively short periods, and incidence rates vary widely across geographic areas. These observations suggest that environmental factors, broadly defined, account for much of the disease (*27*). Temporal and spatial variations in disease frequency, however, are nonspecific with respect to the etiologic agents involved (*28*). Because environmental contaminants that are diabetogenic in humans are plausible, we will consider the evidence that any might be associated with risk of diabetes. In our discussion we briefly address whether the variation in rates of diabetes in the Areas of Concern might be related to the contaminants identified in this review.

Potential Risk Factors for Type 1 Diabetes

Nitrates, Nitrites, and Nitrosoamines

In the gastrointestinal tract, nitrates can be converted to nitrites, and nitrites can react with amines to form *N*-nitroso compounds. Because of this interrelatedness, we have considered the data for these nitrogen-containing compounds together. Drinking water can be contaminated with nitrates resulting from fertilizer application. Foods contain nitrates, nitrites, and *N*-nitroso compounds.

In 1981 Helgason and Jonasson (*29*) first drew attention to the possibility that *N*-nitroso compounds may cause type 1 diabetes in humans. Consumption early in pregnancy of cured mutton, a source of *N*-nitroso compounds, was followed by a high incidence of type 1 diabetes in male offspring. They proposed that dietary nitrosamine activity was inhibited by estrogen and promoted by testosterone, as with streptozotocin, thus accounting for the male specificity. Helgason et al. (*30*) subsequently induced diabetes in the progeny of mice fed *N*-nitroso–laden mutton, and males were preferentially affected. Subsequent *in vitro* work revealed that selected *N*-nitroso compounds were especially toxic to pancreatic β cells (*31*).

Associations between regional water nitrate levels and the incidence of type 1 diabetes have been reported in three ecologic studies (Table 1). Kostraba et al. (*3*) found a positive correlation even though the range of average nitrate levels was relatively limited. The association, however, appeared to be influenced greatly by data from one or two counties. Parslow et al. (*32*) reported that the rate of diabetes was 30% higher among those in water supply zones with average nitrate levels of 14.9–40 mg/L compared with those in areas with means less than 3.2 mg/L. Van Maanen et al. (*33*) reported a 50% increase in rates when nitrate levels exceeded 25 mg/L, compared with levels less than 10 mg/L, though the confidence interval (CI) for this increase was wide and included one. The average nitrate concentrations in all areas of all three studies were below the current World Health Organization standard (50 mg/L) (*34*). Although the data from these studies are consistent with the nitrate hypothesis, they provide only modest support because of the possibility that correlates of water nitrate level could account for the associations observed. This possibility is better addressed by data from case–control studies. In addition, drinking water exposure data could possibly be improved if seasonal variation in nitrate levels were assessed.

Data from case–control studies on childrens' dietary intakes of nitrogen-containing compounds and type 1 diabetes (*35–37*) show a mixture of results (Table 2). Virtanen et al. (*36*) estimated intake of nitrate and nitrite from drinking water and found no relation with risk (not shown in table). The intake of nitrates and nitrites from food was much greater than from water (*36*). Because the absolute intake of *N*-nitroso compounds, nitrates, and nitrites was not reported in most studies (*35,37*), it is possible that low exposure levels in some studies was responsible for lack of association (*37*). A further uncertainty is whether nitrate is equally toxic in food and in water.

In summary, some data suggest an association between intake of nitrogen-containing compounds and risk of type 1 diabetes. Overall, however, the data are limited and inconsistent.

Polychlorinated Biphenyls

In a recent small study of pregnant women, serum levels of PCBs were 30% higher among those with diabetes (primarily type 1) than among those without (*38*). Because the study was cross-sectional, whether the association was causal could not be determined. If the association is confirmed by others, studies designed to assess whether the association is causal would be in order.

Table 1. Summary of results from ecologic studies of average water nitrate levels in relation to incidence of type 1 diabetes.

First author, year	Site	Number of geographic units	Exposure levels (mg/L)	Results	Comments
Kostraba, 1992 (*3*)	Colorado, United States	63 Counties	0 – 8.2	$r = 0.23$	$p = 0.07$; 2 influential counties
Parslow, 1997 (*32*)	Yorkshire, United Kingdom	148 Water supply zones	1.5 – <3.2 3.2 – <14.9 14.9 – 41.0	*RR* 1 *RR* 1.1 *RR* 1.3*	
Van Maanen, 2000 (*33*)	The Netherlands	3,932 Postal code areas	<10 10 – 25 >25	*RR* 1 *RR* 1.0 *RR* 1.5	

Abbreviations: *r*, Pearson correlation coefficient; *RR*, relative risk. *$p < 0.05$.

Table 2. Summary of results from case–control studies of dietary nitrates, nitrites, and nitrosamines in relation to type 1 diabetes.

First author, year	Site	Number of cases	Exposure	Exposure quartile	Odds ratio
Dalquist, 1990 (*35*)	Sweden	339	Nitrosamine in food	1	1
				2–3	1.7*
				4	2.6*
			Nitrate and nitrite in food	1	1
				2–3	0.8
				4	2.4*
Virtanen, 1993 (*36*)	Finland	684	Nitrite in food	1	1
				2	1.2
				3	1.5*
				4	2.3*
			Nitrate in food	1	1
				2	0.8
				3	1.0
				4	0.9
Verge, 1994 (*37*)	Australia	217	Nitrosamine in food	1	1
				2[a]	0.7
				3	1.1

[a]Verge et al. (*37*) used tertiles. *$p < 0.05$.

Potential Risk Factors for Type 2 Diabetes

Arsenic

Epidemiologic data for populations with high exposure to arsenic, including selected industrial groups, are generally consistent with an increased risk of type 2 diabetes (Table 3). In several studies of other populations with high arsenic exposure, investigators have not specifically reported results for diabetes (*44–47*), raising the possibility that no notable associations were present.

Compared with the arsenic exposure levels among the populations represented in Table 3 (*4,39,40*), exposure levels in the general U.S. population are much lower, with a mean drinking water level of about 0.001 mg/L (*48*). Within the United States, some areas have higher levels of exposure, for example, in parts of Utah where the average water arsenic levels are roughly 0.1 mg/L (*49*). A study among the Utah population that had increased exposure (*49*) showed that the overall rate of death from diabetes was not increased compared with the rate from the rest of Utah.

Arsenic is metabolized *in vivo* to trivalent arsenic. A trivalent arsenical, phenylarsine oxide, has adverse effects on the insulin receptor and glucose transport in *in vitro* experiments (*50*).

The available epidemiologic data on arsenic and diabetes are suggestive but inconclusive because of the limited number of studies, their small size, and the possibility of publication bias. The available data do not address the dose–response issue in detail. If arsenic exposure via drinking water does increase risk of type 2 diabetes, this may occur only among those consuming water with an arsenic concentration of more than 0.1 mg/L. This is potentially an extremely serious problem in Bangladesh, where up to 30 million people may be drinking arsenic-contaminated water (*51*).

Table 3. Risk of type 2 diabetes in groups highly exposed to arsenic relative to less-exposed groups, by type of exposure.

First author, year	Place or type	Number of exposed cases	Mean exposure level[a,b]	*RR*[a]	Study design
Exposure via drinking water					
Tseng, 2000 (*39*)	Taiwan	41	0.8 mg/L water	4*	Ecologic
Tsai, 1999 (*40*)	Taiwan	188	0.8 mg/L water	1.4*	Ecologic[c]
Rahman, 1998 (*4*)	Bangladesh	21	0.5 mg/L water	6*	Cross-sectional
Occupational exposure					
Rahman, 1995 (*41*)	Copper smelter	10	0.5 mg/m^3 air	4	Nested case–control
Rahman, 1996 (*42*)	Glass workers	31	Unknown	1.4	Nested case–control
Bartoli, 1998 (*43*)	Glass workers	3	Unknown	0.34[d]	Occupational cohort

[a]Approximate. [b]Among the exposed group. [c]The subjects in the Tseng et al. study (*39*) and Tsai et al. study (*40*) overlapped somewhat (Putai Township). [d]Value shown is reported SMR/100.* $p < 0.05$.

Table 4. Description of studies on TCDD in relation to type 2 diabetes or hyperglycemia.

First author, year	Exposure level	Number exposed: Total	Number exposed: With diabetes	Association	Outcome
Pazderova-Vejlupkova, 1981 (*52*)	High	55	11	+	GTT[a]
Suskind, 1984 (*53*)	High	200		∅	Glucose
Ott, 1994 (*54*)	High	134		±	Glucose
Zober, 1994 (*55*)	High	158	10	–	Diabetes
Henriksen, 1997 (*56*)	Medium	989	146	+	Diabetes, GTT
Calvert, 1999 (*57*)	High	281	26	±	Diabetes, glucose
Pesatori, 1998 (*58*)	High		132	+	Mortality[b]
Vena, 1998 (*59*)	High		33	±	Mortality
Steenland, 1999 (*60*)	High		89	∅	Mortality
Longnecker, 2000 (*5*)	Low	1,197	169	+	Diabetes, GTT
Cranmer, 2000 (*61*)	Low–moderate	69		+	Insulin, GTT[c]

Abbreviations: –, inverse relation; ∅, no association; ±, equivocally positive association; +, unequivocally positive association. [a]Study design was case series; $n = 1$ based on one-fifth of cases with abnormal GTT. [b]Results for females were unequivocally positive. [c]Increased insulin level was the positive finding.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

We identified 11 reports that addressed the relation of TCDD with type 2 diabetes, hyperglycemia, or hyperinsulinemia (Table 4). Most of the studies were of workers exposed to TCDD (*52–55,57,59,60*). Cranmer et al. (*61*) studied community members living near a toxic waste disposal site, and Pesatori et al. (*58*) reported on the experience of those living near a TCDD-laden plume resulting from an out-of-control reaction in a chemical plant. Vietnam veterans exposed to TCDD in Agent Orange were the subjects in the report by Henriksen et al. (*56*). A group of veterans not exposed to Agent Orange were the subjects in the report by Longnecker and Michalek (*5*). We excluded from this review two studies that examined diabetes in veterans who had served in the Vietnam War but for whom no serum TCDD levels were available (*62,63*). Most Vietnam veterans were not exposed to TCDD more than other groups with background-level exposure (*64,65*); exceptions were veterans in the Chemical Core and in Operation Ranch Hand who came in contact with Agent Orange.

The results of the 11 studies were categorized according to type of outcome and exposure level (Table 5). Of the studies showing an unequivocally positive association, none are very convincing on close examination.

The results from the Seveso study (*58*) were unequivocally positive among women but not among men. The relative risk of 1.9 (95% CI, 1.1–3.2) among the highly exposed women in Zone B was adjusted for age but not other risk factors.

The group of highly exposed Czech workers (mean age 46 years) (*52*) had a higher prevalence of diabetes than those 20–79 years of age in the Czech Republic (*24*). But in the absence of a statistical comparison of prevalences and the possibility that confounding factors accounted for the increase, whether the prevalence of diabetes was notably greater than expected remains in doubt.

Although the study by Henriksen et al. (*56*) was a cohort study, the TCDD serum levels used to assess exposure were measured within a few years of when diabetes and related outcomes were ascertained. Thus, if diabetics or subjects with subclinical glucose intolerance had a slower rate of excretion of TCDD, this could account for the association observed (*66*). Furthermore, the prevalence of diabetes in veterans exposed to Agent Orange was not greater than in the unexposed comparison group. The results from the study by Longnecker and Michalek (*5*) suffer from the same weakness outlined for the study by Henriksen et al. (*56*).

The positive finding in the study by Cranmer et al. (*61*) was an association of TCDD level with hyperinsulinemia on a glucose tolerance test (GTT). Although this is consistent with a TCDD–type 2 diabetes relation, no association with glucose was found.

Table 5. A tally of study results on TCDD in relation to type 2 diabetes or hyperglycemia.[a]

	Association: –	∅	±	+
Mortality studies				
Medium–high exposed		|	|	|
Morbidity studies				
Low–moderate exposed				||
Medium–high exposed	|	|	||	||

Abbreviations: –, inverse relation; ∅, no association; ±, equivocally positive association; +, unequivocally positive association. [a]The studies from which results were tallied are listed in Table 4.

Several of the studies with equivocally positive results also have notable weaknesses. The populations studied by Ott et al. (*54*) and Zober et al. (*55*) were basically the same, but the results of these two studies appear to be inconsistent with each other (Table 4). Calvert et al. (*57*) found that the workers with the highest serum TCDD levels also had the highest serum glucose levels compared with those of an unexposed group, but within the group of exposed workers there was no dose–response relation between TCDD levels and serum glucose or prevalence of diabetes.

Overall, the data on TCDD exposure in relation to diabetes and hyperglycemia are mixed. Compelling studies supporting a causal effect of TCDD on diabetes are absent. We note, however, that Enan et al. (*67*) have shown that TCDD decreases cellular glucose update, thus a diabetogenic effect of TCDD is biologically plausible.

Occupational Exposures

In this section we review data on diabetes in relation to occupational exposures. Data for workers exposed to arsenic and TCDD, however, were considered above with the relevant nonoccupational data. The statistical power of occupational mortality studies, such as those shown in Table 6, to detect increases due to diabetogenic exposures is limited because *a*) reporting of diabetes on death certificates is highly variable and death certificates reflect less than half of the diabetes among the deceased (*80*), *b*) the assessment of exposure may lack sufficient detail, and *c*) the number of exposed subjects who develop diabetes is relatively small in typical occupational cohort studies. In addition, exposures in the occupational setting are generally mixed and not specific with respect to toxic substances implicated.

Among rubber workers, a moderately increased mortality from diabetes was reported in two cohorts (*68,69,81*). Two subgroups of rubber workers were identified by McMichael and colleagues (*69,81*) as having the greatest risk of diabetes: *a*) those in inspection, finishing, and repair, and *b*) those in janitoring, trucking, power plant, and test driving. In the report by Andjelkovic et al. (*69*), the overall standardized mortality ratio (SMR) for diabetes was only slightly elevated at 117, but when the deaths occurring only during retirement were considered, the SMR was 135 ($p < 0.05$). Similarly, Weiland and colleagues (*70*) found that mortality from diabetes was greater among retired rubber workers (SMR = 181; 95% CI, 131–244) than among active workers (SMR = 152; 95% CI, 112–201). The greater risk of occupation-associated diabetes seen after retirement (*69,70*) fits with the hypothesis that an occupation-induced susceptibility to type 2 diabetes could be unmasked by the increased sedentarism and obesity that accompany retirement. Exposure to *N*-nitroso compounds in the rubber industry has been high (*82*), although exposure to other agents such as β-naphthylamine, benzene, polycyclic aromatic hydrocarbons, solvents, fumes from vulcanization, and talc has also been frequent.

Data on mortality from diabetes among pulp and paper mill workers have been presented in three reports (*71–73*), with a moderate excess of diabetes evident in two (*71,72*). Although exposure to numerous chemicals and other substances occurs in the pulp and paper industry, potentially notable agents are dioxins and talc.

Among a group of chemical industry workers, deaths from diabetes were double the expected number (*74*). Among the many exposures in that group, none were specifically linked to diabetes. In a smaller study among chemical and refinery workers, there was no overall excess of diabetes (*75*). Among the subset who did at least some work in the chemical plant, however, an SMR of 173 was found, although this was not statistically significant (three observed cases).

Dry-cleaning workers have been exposed to several solvents, with tetrachloroethylene the main agent in use since the 1950s (*77*). In the two studies of laundry and dry-cleaning workers reporting results specifically for diabetes, an excess of death from diabetes was found in one study (*76*) but not in a second smaller one (*77*).

Excess mortality from diabetes was also found among workers involved in engine manufacturing (*78*). Exposure specifically to machining fluid was associated with increased risk. Some machining fluids contain *N*-nitroso compounds, but the straight oils implicated in this study did not.

In a study of a group of pesticide users and an unexposed group, Morgan et al. (*79*) found that subjects with diabetes, compared with those without diabetes, had higher blood levels of 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) and its metabolite 1,1-trichloro-2,2-bis(*p*-chlorophenyl) ethylene (DDE). As with the studies of TCDD, the possibility exists that subjects with diabetes or prediabetes excreted organochlorines (in this case DDT and DDE) more slowly.

An excess of diabetes has also been reported among workers exposed to heat stress (*83*) and among those with sedentary occupations (*81,84*). Because these associations were likely due to confounding by body mass index or low physical activity, we considered them outside the scope of this review.

Trivalent chromium is an essential nutrient, and supplementation improves glucose tolerance in most clinical trials (*85*). A study of tannery workers occupationally exposed to chromium found a lower prevalence of impaired glucose tolerance and of diabetes mellitus than in the control group, even though the exposed workers were more obese; the results, however, were statistically significant only among workers more than 48 years of age (*86*). In other studies of chromium-exposed tannery workers, investigators have generally not presented results for diabetes (*87,88*), although in one study exposed workers had an SMR of 130 (95% CI, 67–227) (*89*).

In summary, the occupational data show for both rubber and pulp and paper mill workers an excess of diabetes deaths in more than one study (*68,70–72*), but results were mixed (*69,73*). Complete investigations of occupational risks would need to account for the level of physical activity and body mass index associated with a given exposure.

Table 6. Summary of data on diabetes in selected occupational groups.

First author, year	Industry/occupation	Number of cases	SMR
McMichael, 1974 (*68*)	Rubber	43	143*
Andjelkovic, 1976 (*69*)	Rubber	48	117
Weiland, 1996 (*70*)	Rubber	49	152*
Schwartz, 1988 (*71*)	Pulp, paper mill	22	146*,[a]
Wingren, 1991 (*72*)	Pulp, paper mill	46	130*,[b]
Wong, 1996 (*73*)	Pulp, paper mill	17	110
Wong, 1984 (*74*)	Chemical	19	220*
Marsh, 1991 (*75*)	Chemical, refinery	9	77
Katz, 1981 (*76*)	Laundry, dry cleaning	25	177*,[a]
Blair, 1979 (*77*)	Laundry, dry cleaning	9	103[a]
Park, 1996 (*78*)	Engine manufacturing	25	150*,[a]
Morgan, 1980 (*79*)	Pesticide users	58	>100*,[c]

[a]Proportional mortality ratio. [b]Originally presented as an odds ratio; here shown ×100. [c]DDE/DDT levels in cases significantly higher than in controls. No SMR or *RR* was presented, but presumably if one had been presented, it would be greater than 100 if expressed on a scale comparable with the others shown in the table. *$p < 0.05$.

Discussion

Environmental Contaminants and Increased Rates of Diabetes

Available data on drinking water nitrates do not exclude the possibility that nitrates affect risk of type 1 diabetes, but neither were they strongly supportive of an association. More

data from case–control studies done in areas where exposure to nitrates in water is unusually high would be particularly useful.

The association between PCBs and type 1 diabetes was reported in only one small cross-sectional study. The importance of this observation will be clearer if replicated by others, especially using a prospective design.

Data on health effects of arsenic were suggestive of an association with type 2 diabetes. Additional reports on diabetes in groups consuming water contaminated with arsenic, where epidemiologic studies of other outcomes have already been done (*44–47*), could be useful. If an arsenic effect exists, however, it is likely to affect few populations because severe contamination is unusual.

TCDD appeared to be the only environmental contaminant identified that could be having widespread affects in the general population. But data among populations with background-level exposure came from just two studies, each with limitations. Prospective data on the relation between TCDD and type 2 diabetes are needed.

Although selected occupational exposures may increase risk of type 2 diabetes, few specific agents were implicated in our review. Additional data on diabetes among those with exposure to *N*-nitroso compounds, arsenic, TCDD, talc, and straight oil machining fluids would be of interest.

Environmental Contaminants and Local Variation in Rates of Diabetes

The observation that prompted this review was that hospitalization rates for diabetes varied across the Areas of Concern (*1*). The great majority of diabetes is type 2; therefore, the variation in hospitalization rates is accounted for by corresponding variation either in risk factors for type 2 diabetes or in the medical management of patients. Given that relative body weight is such a strong risk factor for type 2 diabetes, it is highest among the potential suspects accounting for geographic variation in rates of diabetes. Without the ability to take this and other such accepted risk factors for diabetes into account, it would be highly speculative to assume a high rate of diabetes in a given area was due to contamination.

Nonetheless, areas with higher rates of hospitalization could be those containing a substantial portion of the population occupationally exposed to a diabetogenic agent. Among the studies where an occupation was associated with an increased rate of death from diabetes, however, the rate was at most doubled and was usually much lower. An investigation of diabetes among workers involved in engine manufacturing, as in the Park and Mirer study (*78*), taking occupational physical activity into account, may be worthwhile. (Windsor, Ontario, Canada, one of the Areas of Concern, had an increase in diabetes hospitalizations, is economically like Detroit, and could have this industry there.) Arsenic exposure from drinking water in the Areas of Concern would seem an unlikely culprit, but the possibility of occupational arsenic exposure might be worth investigating. Similarly, substantial variation in contamination of the food supply with TCDD seems unlikely, but again, the possibility of occupational exposure may be worth considering.

β-Cell Toxins and Type 2 Diabetes

Type 1 and type 2 diabetes have no established risk factors in common (see above). In searching for new risk factors, however, it may be worthwhile to consider that there could be overlap in the risk factors for these two types of diabetes. Both type 1 and type 2 diabetes have β-cell insufficiency, to a greater or lesser extent, as part of their pathogenesis. The β-cell toxin streptozotocin, typically used to induce type 1 diabetes in animals, under certain conditions can cause type 2 diabetes (*90*). Thus, for example, examining nitrosamine intake as a risk factor for type 2 diabetes could be worthwhile.

Summary

With respect to variation in diabetes rates in the Areas of Concern, our review points to no obvious environmental contaminants that might explain the variation in diabetes rates. Several occupations and occupational exposures were identified, however, that may have contributed. In general terms regarding environmental contaminants as etiologic agents for diabetes, data on arsenic and TCDD were suggestive but inconclusive with respect to type 2 diabetes, and for type 1 diabetes data on intake of nitrates, nitrites, and *N*-nitroso compounds were less suggestive but not completely null. Apart from the exposures considered in this review, other environmental contaminants could be related to risk of diabetes; however, no specific clues were uncovered in the epidemiologic literature.

References and Notes

1. Elliot S, Eyles J, DeLuca P. Mapping health in the Great Lakes Areas of Concern: a user-friendly tool for policy and decision makers. Environ Health Perspect 109(suppl 6):817–826 (2001).
2. United States and Canada. Great Lakes Water Quality Agreement, 1972. *http://www.on.ec.gc.ca/glwqa* [cited 9 November 2001].
3. Kostraba JN, Gay EC, Rewers M, Hamman RF. Nitrate levels in community drinking waters and risk of IDDM. Diabetes Care 15:1505–1508 (1992).
4. Rahman M, Tondel M, Ahmad SA, Axelson O. Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol 148:198–203 (1998).
5. Longnecker MP, Michalek JE. Serum dioxin level in relation to diabetes mellitus among Air Force veterans with background levels of exposure. Epidemiology 11:44–48 (2000).
6. Franco G, Malamani T, Piazza A. Glucose tolerance and occupational exposure to carbon disulphide [Letter]. Lancet 2:1208 (1978).
7. Wareham NJ, O'Rahilly S. The changing classifiication and diagnosis of diabetes. New classifiication is based on pathogenesis not insulin dependence. Br Med J 317:359–360 (1998).
8. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. A study of 200 pairs. Diabetologia 20:87–93 (1981).
9. Kaprio J, Tuomilehto J, Koskenvuo M, Romanov K, Reunanen A, Eriksson J, Stengard J, Kesaniemi YA. Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 35:1060–1067 (1992).
10. Dahlquist G. Environmental risk factors in human type 1 diabetes—an epidemiological perspective. Diabetes Metab Rev 11:37–46 (1995).
11. Karam JH, Lewitt PA, Young CW, Nowlain RE, Frankel BJ, Fujiya H, Freedman ZR, Grodsky GM. Insulinopenic diabetes after rodenticide (Vacor) ingestion: a unique model of acquired diabetes in man. Diabetes 29:971–978 (1980).
12. Assan R, Perronne C, Assan D, Chotard L, Mayaud C, Matheron S, Zucman D. Pentamidine-induced derangements of glucose homeostasis. Determinant roles of renal failure and drug accumulation. A study of 128 patients. Diabetes Care 18:47–55 (1995).
13. Peschke E, Ebelt H, Bromme HJ, Peschke D. 'Classical' and 'new' diabetogens—comparison of their effects on isolated rat pancreatic islets *in vitro*. Cell Mol Life Sci 57:158–164 (2000).
14. Nathan DM. Diabetes mellitus. In: Scientific American Medicine (Rubenstein E, Federman DD, eds). New York: Scientifiic American, 1997.
15. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of type 1 diabetes—the analysis of the data on published incidence trends. Diabetologia 42:1395–1403 (1999).
16. Bodington MJ, Muzulu SI, Burden AC. Spatial clustering in childhood diabetes: evidence of an environmental cause. Diabet Med 12:865–867 (1995).
17. Dahlquist GG, Kallen BA. Time-space clustering of date at birth in childhood-onset diabetes. Diabetes Care 19:328–332 (1996).
18. Law GR, McKinney PA, Staines A, Williams R, Kelly M, Alexander F, Gilman E, Bodansky HJ. Clustering of childhood IDDM. Links with age and place of residence. Diabetes Care 20:753–756 (1997).
19. O'Rahilly S. Science, medicine, and the future. Non-insulin dependent diabetes mellitus: the gathering storm. Br Med J 314:955–959 (1997).
20. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039–1057 (1979).
21. Kadowaki T. Insights into insulin resistance and type 2 diabetes from knockout mouse models. J Clin Investig 106:459–465 (2000).
22. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS. Diabetes trends in the US: 1990-1998. Diabetes Care 23:1278–1283 (2000).
23. Trends in the prevalence and incidence of self-reported diabetes mellitus—United States, 1980-1994. Morb Mortal Wkly Rep 46:1014–1018 (1997).
24. International Diabetes Federation. Diabetes Atlas 2000. Brussels, Belgium:International Diabetes Federation, 2000.
25. Bloomgarden ZT. European Association for the Study of Diabetes Annual Meeting, 1999: complications of diabetes. Diabetes Care 23:1423–1428 (2000).
26. Mandrup-Poulsen T. Diabetes. Br Med J 316:1221–1225 (1998).
27. Diabetes Epidemiology Research International. Preventing insulin dependent diabetes mellitus: the environmental challenge. Br Med J (Clin Res Ed) 295:479–481 (1987).
28. Morgenstern H. Ecologic studies in epidemiology: concepts, principles, and methods. Annu Rev Public Health 16:61–81 (1995).
29. Helgason T, Jonasson MR. Evidence for a food additive as a cause of ketosis-prone diabetes. Lancet 2:716–720 (1981).
30. Helgason T, Ewen SWB, Ross IS, Stowers JM. Diabetes produced in mice by smoked/cured mutton. Lancet 2:1017–1022 (1982).
31. Wilson GL, Mossman BT, Craighead JE. Use of pancreatic beta cells in culture to identify diabetogenic *N*-nitroso compounds. In Vitro 19:25–30 (1983).
32. Parslow RC, McKinney PA, Law GR, Staines A, Williams R, Bodansky HJ. Incidence of childhood diabetes mellitus in Yorkshire, northern England, is associated with nitrate in drinking water: an ecological analysis. Diabetologia 40:550–556 (1997).
33. van Maanen JM, Albering HJ, de Kok TM, van Breda SG, Curfs DM, Vermeer IT, Ambergen AW, Wolffenbuttel BH, Kleinjans JC, Reeser HM. Does the risk of childhood diabetes mellitus require revision of the guideline values for nitrate in drinking

water. Environ Health Perspect 108:457–461 (2000).
34. WHO. Inorganic constituents and physical parameters. In: Guidelines for Drinking Water Quality, Vol 2: Health Criteria and Other Supporting Information, 2nd ed. Geneva:World Health Organization, 1996;313–324.
35. Dahlquist GG, Blom LG, Persson L, Sandstrom AIM, Wall SGI. Dietary factors and the risk of developing insulin dependent diabetes in childhood. Br Med J 300:1302–1306 (1990).
36. Virtanen SM, Jaakkola L, Rasanen L, Ylonen K, Aro A, Lounamaa R, Akerblom HK, Tuomilehto J. Nitrate and nitrite intake and the risk for type 1 diabetes in Finnish children. Childhood Diabetes in Finland Study Group. Diabet Med 11:656–662 (1994).
37. Verge CF, Howard NJ, Irwig L, Simpson JM, Mackerras D, Silink M. Environmental factors in childhood IDDM. A population-based, case-control study. Diabetes Care 17:1381–1389 (1994).
38. Longnecker MP, Klebanoff MA, Brock JW, Zhou H. Polychlorinated biphenyl serum levels in pregnant subjects with diabetes. Diabetes Care 24:1099–1101 (2001).
39. Tseng CH, Tai TY, Chong CK, Tseng CP, Lai MS, Lin B, Chiou HY, Hsueh YM, Hsu KH, Chen CJ. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan. Environ Health Perspect 108:847–851 (2000).
40. Tsai SM, Wang TN, Ko YC. Mortality for certain diseases in areas with high levels of arsenic in drinking water. Arch Environ Health 54:186–193 (1999).
41. Rahman M, Axelson O. Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. Occup Environ Med 52:773–774 (1995).
42. Rahman M, Wingren G, Axelson O. Diabetes mellitus among Swedish art glass workers—an effect of arsenic exposure? Scand J Work Environ Health 22:146–149 (1996).
43. Bartoli D, Battista G, De Santis M, Iaia TE, Orsi D, Tarchi M, Pirastu R, Valiani M. Cohort study of art glass workers in Tuscany, Italy: mortality from non-malignant diseases. Occup Med 48:441–445 (1998).
44. Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. Am J Epidemiol 147:660–669 (1998).
45. Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. Int J Epidemiol 27:561–569 (1998).
46. Cuzick J, Sasieni P, Evans S. Ingested arsenic, keratoses, and bladder cancer. Am J Epidemiol 136:417–421 (1992).
47. Tsuda T, Nagira T, Yamamoto M, Kume Y. An epidemiological study on cancer in certified arsenic poisoning patients in Toroku. Ind Health 28:53–62 (1990).
48. IARC. Some metals and metallic compounds. IARC Monogr Eval Carcinog Risk Chem Hum 23:69 (1980).
49. Lewis DR, Southwick JW, Ouellet-Hellstrom R, Rench J, Calderon RL. Drinking water arsenic in Utah: a cohort mortality study. Environ Health Perspect 107:359–365 (107).
50. Douen AG, Jones MN. Phenylarsine oxide and the mechanism of insulin-stimulated sugar transport. Biofactors 2:153–161 (1990).
51. Hoque BA, Mahmood AA, Quadiruzzaman M, Khan F, Ahmed SA, Shafique SA, Rahman M, Morshed G, Chowdhury T, Rahman MM, et al. Recommendations for water supply in arsenic mitigation: a case study from Bangladesh. Public Health 114:488–494 (2000).
52. Pazderova-Vejlupkova J, Lukas E, Nemcova M, Pickova J, Jirasek L. The development and prognosis of chronic intoxication by tetrachlordibenzo-*p*-dioxin in men. Arch Environ Health 36:5–11 (1981).
53. Suskind RR, Hertzberg VS. Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251:2372–2380 (1984).
54. Ott MG, Zober A, Germann C. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. Chemosphere 29:2423–2437 (1994).
55. Zober A, Ott MG, Messerer P. Morbidity follow up study of BASF employees exposed to 2,3,7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) after a 1953 chemical reactor incident. Occup Environ Med 51:479–486 (1994).
56. Henriksen GL, Ketchum NS, Michalek JE, Swaby JA. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 8:252–258 (1997).
57. Calvert GM, Sweeney MH, Deddens J, Wall DK. Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Occup Environ Med 56:270–276 (1999).
58. Pesatori AC, Zocchetti C, Guercilena S, Consonni D, Turrini D, Bertazzi PA. Dioxin exposure and non-malignant health effects: a mortality study. Occup Environ Med 55:126–131 (1998).
59. Vena J, Boffetta P, Becher H, Benn T, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Green L, Kauppinen T, et al. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. Environ Health Perspect 106(suppl 2):645–653 (1998).
60. Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. J Natl Cancer Inst 91:779–786 (1999).
61. Cranmer M, Louie S, Kennedy RH, Kern PA, Fonseca VA. Exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is associated with hyperinsulinemia and insulin resistance. Toxicol Sci 56:431–436 (2000).
62. CDC. The Centers for Disease Control Vietnam Experience Study. Health status of Vietnam veterans. II: Physical health. JAMA 259:2708–2714 (1988).
63. Commonwealth Department of Veterans' Affairs. Morbidity of Vietnam Veterans: a Study of the Health of Australia's Vietnam Veteran Community. Vol 1: Male Vietnam Veterans Survey and Community Comparison Outcomes. Canberra:Commonwealth Department of Veterans' Affairs, 1998.
64. CDC. The Centers for Disease Control Veterans Health Studies. Serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels in U.S. Army Vietnam-era veterans. JAMA 260:1249–1254 (1988).
65. Gladen BC, Longnecker MP, Schecter AJ. Correlations among polychlorinated biphenyls, dioxins, and furans in humans. Am J Ind Med 35:15–20 (1999).
66. Flanders WD, Lin L, Pirkle JL, Caudill SP. Assessing the direction of causality in cross-sectional studies. Am J Epidemiol 135:926–935 (1992).
67. Enan E, Lasley B, Stewart D, Overstreet J, Vandevoort CA. 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) modulates function of human luteinizing granulosa cells via cAMP signaling and early reduction of glucose transporting activity. Reprod Toxicol 10:191–198 (1996).
68. McMichael AJ, Spirtas R, Kupper LL. An epidemiologic study of mortality within a cohort of rubber workers, 1964-72. J Occup Med 16:458–464 (1974).
69. Andjelkovic D, Taulbee J, Symons M. Mortality experience of a cohort of rubber workers, 1964-1973. J Occup Med 18:387–394 (1976).
70. Weiland SK, Mundt KA, Keil U, Kraemer B, Birk T, Person M, Bucher AM, Straif K, Schumann J, Chambless L. Cancer mortality among workers in the German rubber industry: 1981-91. Occup Environ Med 53:289–298 (1996).
71. Schwartz E. A proportionate mortality ratio analysis of pulp and paper mill workers in New Hampshire. Br J Ind Med 45:234–238 (1988).
72. Wingren G, Persson B, Thoren K, Axelson O. Mortality pattern among pulp and paper mill workers in Sweden: a case-referent study. Am J Ind Med 20:769–774 (1991).
73. Wong O, Ragland DR, Marcero DH. An epidemiologic study of employees at seven pulp and paper mills. Int Arch Occup Environ Health 68:498–507 (1996).
74. Wong O, Brocker W, Davis HV, Nagle GS. Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB, and DDT. Br J Ind Med 41:15–24 (1984).
75. Marsh GM, Enterline PE, McCraw D. Mortality patterns among petroleum refiiery and chemical plant workers. Am J Ind Med 19:29–42 (1991).
76. Katz RM, Jowett D. Female laundry and dry cleaning workers in Wisconsin: a mortality analysis. Am J Public Health 71:305–307 (1981).
77. Blair A, Decouflle P, Grauman D. Causes of death amng laundry and dry cleaning workers. Am J Public Health 69:508–511 (1979).
78. Park RM, Mirer FE. A survey of mortality at two automotive engine manufacturing plants. Am J Ind Med 30:664–673 (1996).
79. Morgan DP, Lin LI, Saikaly HH. Morbidity and mortality in workers occupationally exposed to pesticides. Arch Environ Contam Toxicol 9:349–382 (1980).
80. Andresen EM, Lee JA, Pecoraro RE, Koepsell TD, Hallstrom AP, Siscovick DS. Underreporting of diabetes on death certifiicates, Kin County, Washington. Am J Public Health 83:1021–1024 (1993).
81. McMichael AJ, Spirtas R, Gamble JF, Tousey PM. Mortality among rubber workers: relationship to specific jobs. J Occup Med 18:178–185 (1976).
82. Spiegelhalder B, Preussmann R. Occupational nitrosamine exposure 1: rubber and tyre industry. Carcinogenesis 4:1147–1152 (1983).
83. Wojtczak-Jaroszowa J, Jarosz D. Health complaints, sicknesses and accidents of workers employed in high environmental temperatures. Can J Public Health 77(suppl 1):132–135 (1986).
84. Morikawa Y, Nakagawa H, Ishizaki M, Tabata M, Nishijo M, Miura K, Kawano S, Kido T, Nogawa K. Ten-year follow-up study on the relation between the development of non-insulin-dependent diabetes mellitus and occupation. Am J Ind Med 31:80–84 (1997).
85. Mertz W. Chromium in human nutrition: a review. J Nutr 123:626–633 (1993).
86. Stupar J, Vrtovec M, Kocijancic A, Gantar A. Chromium status of tannery workers in relation to metabolic disorders. J Appl Toxicol 19:437–446 (1999).
87. Takahashi K, Okubo T. A prospective cohort study of chromium plating workers in Japan. Arch Environ Health 45:107–111 (1990).
88. Pastides H, Austin R, Lemeshow S, Klar J, Mundt KA. A retrospective-cohort study of occupational exposure to hexavalent chromium. Am J Ind Med 25:663–675 (1994).
89. Montanaro F, Ceppi M, Demers PA, Puntoni R, Bonassi S. Mortality in a cohort of tannery workers. Occup Environ Med 54:588–591 (1997).
90. Hemmings SJ, Spafford D. Neonatal STZ model of type II diabetes mellitus in the Fischer 344 rat: characteristics and assessment of the status of the hepatic adrenergic receptors. Int J Biochem Cell Biol 32:905–919 (2000).