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.

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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 (Rehm 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 monoyzgous 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 non-specific 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.

### 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 RR 1 | RR 1.1 |
| Van Maanen, 2000 (33) | The Netherlands | 3,932 Postal code areas | <10 | RR 1 |
|                     |      |                            | 10 – 25 RR 1.0        |         |
|                     |      |                            | >25 RR 1.5            |         |

Abbreviations: c, 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* |
|                     |       |     | Nitrate in food | 1 | 1 |
|                     |       |     |                      | 2   | 0.8 |
|                     |       |     |                      | 3   | 1.0 |
|                     |       |     |                      | 4   | 0.9 |
| Verge, 1994 (37)    | Australia | 217 | Nitrosamine in food | 1 | 1 |
|                     |       |     |                      | 2a  | 0.7 |
|                     |       |     |                      | 3   | 1.1 |

*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 vitro 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).

2,3,7,8-Tetrachlorodibenzop-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 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[^c] | Study design |
|--------------------|--------------|-------------------------|--------------------------|--------|--------------|
| Table 4. Description of studies on TCDD in relation to type 2 diabetes or hyperglycemia. |

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

| Mortality studies | Morbidity studies |
|-------------------|-------------------|
| Medium–high exposed | Low–moderate exposed | Medium–high exposed |

[^a]: Approximately.  
[^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.
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 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, driving, and testing, 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 only 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.

### 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.

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Park and Mirer study (involved in engine manufacturing, as in the
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Environmental Contaminants and Local Variation in Rates of Diabetes

The observation that prompted this review was that hospitalization rates for diabetes varied

The great majority of diabetes is type 2; therefore, the

variations in diabetes rates are 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

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, nitrates, 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.

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