ABSTRACT. Common environmental chemicals, drugs, or physical agents can adversely affect human teeth during their embryonic development and after their eruption into the oral cavity. One of the more common elemental toxicants is lead. Teeth are known to accumulate lead during their development. Both animal and human studies have shown that teeth with high lead levels are generally more susceptible to dental caries. Similarly, although inorganic fluorides have long been recognized for their potential to prevent dental caries, exposure to excessive amounts of fluoride when enamel is forming often leads to a type of enamel hypoplasia referred to as dental fluorosis or mottled enamel. Teratogenic agents, such as tetracyclines, a class of antibiotic drugs commonly administered to infants and children, will often result in the discoloration of tooth enamel when prescribed during tooth development. It has recently been suggested that childhood exposure to passive smoking increases the risk for dental caries. Environmental tobacco smoke has previously been linked to periodontal disease in adults. However, this is the first report of an association between passive tobacco smoke and increased susceptibility to dental caries. Last, an often-overlooked source of damage to teeth among all age groups after their eruption into the oral cavity is physical trauma from a variety of sources, especially sports-related injuries. Epidemiologic data suggest that up to one third of all dental injuries are sports related. Pediatrics 2004;113:1120–1127; environmental chemicals, drugs, physical agents, tooth development, teeth, dental caries.

ABBREVIATIONS. ETS, environmental tobacco smoke; PAH, polyhalogenated aromatic hydrocarbon; PCB, polychlorinated biphenyl; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Humans have 2 sets of teeth: the primary, or deciduous, dentition followed by the permanent dentition. Primary tooth formation and development usually begins, on average, between the 13th and 16th weeks of gestation for incisors and between the 14th and 24th weeks for canines and molars. Mineralization of the enamel surface is usually complete by the end of the first year of life and root development by 12 to 18 months after eruption. The permanent dentition begins to form in utero, and mineralization is usually complete by age 4 or 5 and root development by 2 to 3 years after eruption. Teeth are most susceptible to developmental disturbances during the mineralization phase of tooth formation. In general, the permanent dentition is more susceptible to disturbances in mineralization by environmental toxicants and drugs than is the primary dentition, most likely as a consequence of its later development. As such, this review focuses on some of the more commonly observed developmental disturbances of the permanent dentition that result from excess exposure to various environmental chemicals and drugs and touches on other, somewhat controversial, toxicants that may adversely affect the child as a whole as well as the dentition. Damage to the teeth from orofacial trauma is also reviewed for its impact on the dentition of both children and adolescents.

ENVIRONMENTAL CHEMICALS

Lead
It has long been known that lead crosses the placenta and has the potential to affect the development of different organ systems, including teeth, and its accumulation in developing teeth has provided a useful record of both fetal and long-term uptake for the study of neuropsychological effect of unidentified childhood exposure to lead. Although clear, unequivocal evidence of a cause-and-effect relationship between embryonic and early childhood exposure to lead and enhanced susceptibility to dental caries is lacking, the preponderance of epidemiologic data, combined with data from animal studies, are suggestive of such a relationship. Bowen described several potential mechanisms on how pre-eruptive exposure to lead could enhance caries risk. However, a dose–response relationship between preeruptive exposure to lead and dental caries has never been determined. Lead has also been shown to accumulate in teeth posteruptively. Although a number of ecological and cross-sectional studies conducted in the 1960s and 1970s implicated posteruptive exposure to lead as a risk factor for caries, the data are not clear that posteruptive exposure to lead has a direct effect on caries susceptibility. A more recent study of the association of dental caries and blood lead levels in children 5 to 17 years of age showed that a 5-μg/dL change in blood lead level was associated with an increased risk for caries and that >2 million excess cases of dental caries in US children may be attributable to environmental lead exposure or factors that are linked to lead exposure. However, as the data were cross-sectional in nature, no temporal or causal relationship could be established. In a study specifically designed to exam-
ine the temporal association between lead exposure and caries, second- and fifth-grade children who were known to have blood levels up to 45 μg/dL (mean: 10.7 μg/dL) as toddlers were not shown to be at greater risk for caries than children who had little or no lead exposure.\textsuperscript{16} As noted by the authors, however, the study had limited statistical power to detect a clinically relevant odds ratio.

Other ways in which lead could have an impact on caries risk revolves around its effect on salivary gland development and function. Work by Watson et al\textsuperscript{17} reported significantly diminished salivary flow rates and subsequent high caries levels in the offspring of laboratory rats whose dams were exposed to 34 ppm lead in the drinking water during pregnancy and during lactation. These observations are currently being followed up in an ongoing clinical study of caries risk resulting from environmental lead exposure in a birth cohort of 245 Cincinnati children who have been participants in the Cincinnati Lead Study since late 1979. This group of black and white Appalachian children is arguably the most well-described longitudinal cohort ever studied for prenatal and postnatal lead exposure, with peak blood levels ranging from 5 to >809 μg/dL.\textsuperscript{18,19} A major goal of this study is to measure potential confounding factors, including dietary habits, oral hygiene, and socioeconomic status, and to assess the influence of these on any observed association between dental caries and lead exposure. If a causal relationship between environmental lead and dental caries is supported, then more aggressive measures for caries prevention could be targeted toward children with high blood lead levels.

**Tobacco**

Several recent studies have reported on the adverse impact of both smoked and smokeless tobacco on the oral health of children, adolescents,\textsuperscript{20–22} and adults.\textsuperscript{23–26} Investigators have specifically linked cigarette smoking with periodontal disease in adults,\textsuperscript{25,27,28} and a relationship between environmental tobacco smoke (ETS) and periodontal health in adults has been reported.\textsuperscript{28} Conversely, only a few studies on the effect of active or passive smoking on oral health, including dental caries and periodontal disease, in children have been reported. No studies have been reported on the effect of maternal active or passive smoking on the preeruptive development of teeth. Data from the 1995 UK National Diet and Nutrition Survey, however, have suggested that maternal but not paternal smoking is a significant risk factor for predicting caries in young children.\textsuperscript{29} Recent work by Aligne et al\textsuperscript{30} based on a secondary analysis of data from the Third National Health and Nutrition Examination Survey (1988–1994) has provided the strongest evidence yet of an increased risk of dental caries in the deciduous dentition of children who are 4 to 11 years of age and have been exposed to ETS. That no effect on permanent teeth was observed is somewhat puzzling, as it would be expected that any effect of ETS on the developing dentition would affect both deciduous and permanent teeth alike. Similarly, if the main effect of ETS is more related to posteruptive forces, then a similar pattern of caries susceptibility in the permanent dentition should be observed. These findings are clearly provocative and beg for aggressive studies that will elucidate the causative role of ETS on the oral health of children and adolescents. Other studies that clearly need to be undertaken revolve around potential mechanisms underlying tobacco’s cariogenic potential. For example, 1 in vitro study suggested that tobacco may have an effect on the growth of oral cariogenic streptococci.\textsuperscript{31} However, the study involved only smokeless tobacco products, and, as the authors noted, growth of cariogenic organisms may have been attributable entirely to the manufacturer’s added sugar and not to natural tobacco sugar. No reported studies have investigated a potential relationship between tobacco in other forms, eg, smoked tobacco, whether active or passive, and growth of cariogenic oral flora. Clearly, much work remains to be undertaken in this area.

**Mercury**

Although the toxic properties of mercury have been well understood for many years, there is no known association between mercury and tooth development or between mercury and dental health. Mercury is an integral component of dental amalgam, a mixture of mercury, tin, silver, zinc, and copper for use as a restorative material in the treatment of dental caries. The major concern with mercury, as used in dentistry, has been the observation that mercury vapor is released from amalgam restorations,\textsuperscript{32–35} and some observers have contended that exposure to mercury from dental amalgam often exceeds the sum of exposure from all other sources.\textsuperscript{36} As 1 of the potential sequelae from mercury toxicity is neurologic damage, studies in both humans and animals have attempted to provide evidence of a relationship between mercury released from dental amalgam and various neurologic disorders, in particular multiple sclerosis.\textsuperscript{37} To date, no credible evidence has been forthcoming on any ill effects from the small amount of mercury released by dental amalgams,\textsuperscript{38,39} including multiple sclerosis.\textsuperscript{40,41} Both the American Dental Association and the US Public Health Service have conducted exhaustive reviews of amalgam safety and concluded that other than rare allergic reactions, mercury from dental amalgam restorations should not be considered harmful to human health when used in the prescribed manner, consistent with American Dental Association and US Public Health Service guidelines and recommendations.\textsuperscript{42–45} Although virtually all human studies on amalgam safety have been conducted in adults, it is unlikely, given the lack of any credible data of adverse effects on adults, that children would differ in their response to mercury vapor release from amalgam fillings. However, the ready availability of large data sets from national oral health surveys of children and young adults over the past 30 years would permit a comparison both between and within cohorts of children from different eras. As caries rates have declined dramatically over the past 30 years and, hence, the placement of fewer amalgam resto-
of nonexposed mothers.48 One study reported a significant association between the duration of breastfeeding and mineralization defects in the first permanent teeth of offspring.49 In this study, mothers did not have known previous occupational or environmental exposure to elevated levels of TCDD and other PCBs, thus suggesting that “background” levels of these compounds could adversely influence dental development. In a follow-up study, the authors went on to suggest that the high frequency of hypomineralized dental defects among the children may be a sign of exposure to dioxin and its congeners, and the presence of defects could potentially be used as a biomarker of exposure.50 More recently, developmental defects in enamel of permanent teeth were reported in 71.3% of children who were exposed long term to PCBs, compared with 49.5% in the control group (P = .0001).51 Overall, these studies seem to suggest that developing oral structures, in particular dental enamel, may be especially susceptible to minute dioxin exposure.

Fluoride

Inorganic fluorides have long been recognized for their potential to reduce the magnitude and the severity of dental caries in children as well as adults.52,53 Although fluoride has substantial benefits in the prevention of tooth decay, depending on the level and source of exposure, fluorides also have adverse effects on human tissues.54 In North America, the major sources of fluoride are from drinking water, beverages, food, and oral hygiene products, including dietary fluoride supplements. The most common adverse effect of excess exposure to fluoride is dental fluorosis, a permanent hypomineralization of enamel, characterized in its mildest form as small, barely visible, white flecks found primarily on cusp tips and on facial surfaces of the permanent dentition.55 The moderate to severe forms, infrequently observed in North America, are found on most permanent tooth surfaces and range between white opaque areas (Fig 1) to darkly stained and pitted enamel.55 The critical window of exposure for fluorosis to manifest occurs during the early maturation stage of tooth development,56 beginning when the child is approximately 2 years of age and continuing for several years thereafter until later-developing teeth have matured.57 Dental fluorosis is a dose–response condition, and the higher the level of exposure during tooth development, the more severe the fluorosis.58–60 In general, fluoride intake during critical periods of tooth development and maturation from approximately birth to 8 years of age is in the range of 0.03 to 0.1 mg F/kg body weight per day.61,62

Although the prevalence of fluorosis has increased during the past 50 years in both optimally fluoridated and fluoride-deficient communities,54 most likely as a result of dietary fluoride supplements,63–69 and to a somewhat lesser extent from the high fluoride content of some infant foods and formulas, especially soy-based formulas,70 and professionally applied topical fluoride solutions or gels,71 the majority of cases are found in the very mild to mild catego-
However, unintentional ingestion of fluoride-containing dentifrices deserves special mention. As pointed out in many recent reports, fluoride-containing toothpastes, particularly when used by toddlers and young children in an unsupervised manner and often in combination with fluoride tablets, can provide another major source of fluoride exposure. Accordingly, toddlers and preschoolers should not have access to fluoride-containing toothpaste. Parents should supervise tooth brushing and should place an amount the size of a pea on the toothbrush.

Dental fluorosis has not been identified as a public health problem in North America. However, given the trend toward the use of agents for whitening teeth and the increased demand for cosmetic dentistry, public rejection of even the mildest form of fluorosis could pose problems for dentistry’s time-tested reliance on this proven and cost-effective caries preventive agent.

**DRUGS**

**Tetracyclines**

Perhaps the best-known and studied interaction between a therapeutic medication and an adverse interaction with tooth development is tetracycline. It has been known for many years that tetracycline has the potential to cause discoloration of teeth and that intensity of discoloration is both time and dose dependent (Fig 2). For example, tetracycline ingestion during periods of enamel calcification either by the mother during gestation or by the child up to approximately age 5 will result in discoloration of the enamel ranging from yellow (tetracycline, demethylchlortetracycline, and oxytetracycline) to gray-brown (chlortetracycline). Oxytetracycline causes the least staining, and doxycycline does not stain at all. Permanent teeth are less intensely stained but more diffusely stained than primary teeth. As timing of administration, dosage, and type of tetracycline all are related to the extent and the type of enamel discoloration, tetracycline administration during pregnancy or periods of enamel calcification should be avoided to the extent possible. In general, tetracycline staining in most of North America is seen only in adults today, rarely in children, as tetracycline is no longer recommended during pregnancy and in young children. One way to differentiate tetracycline staining from other causes of enamel staining is to apply ultraviolet light to the teeth in question. Tetracycline-stained teeth will usually fluoresce. On a final note, it is interesting to point out that chronic ingestion of tetracyclines may cause tooth discoloration, but the antimicrobial effects prevent dental caries as evidenced by earlier observations in children with cystic fibrosis.

**Other Drugs**

There have been many reports over the past several years of prenatal and postnatal administration of anticonvulsants and chemotherapeutic drugs that have an adverse effect on teeth and oral tissues. Studies on medications used for the treatment of childhood cancer and leukemia have consistently
shown that children younger than 5 years at diagnosis and start of treatment exhibit abnormal dental development. The severity of dentofacial-developmental and tooth-related abnormalities secondary to therapy are related to the age of the child, dosage, and duration of treatment. Dental abnormalities include tooth agenesis, arrested root development, microdontia, and enamel disturbances. However, no association between anticancer drugs and increased or decreased risk for dental caries has been reported.

In contrast, though, but not part of this review, radiation therapy for head and neck cancer often results in partial or complete destruction of salivary gland tissues, and, unless extremely aggressive preventive measures are undertaken as part of the overall treatment plan, the onset of acute and rampant dental caries will occur rapidly with devastating consequences to the dentition for both children and adults. Drugs that are used for the treatment of asthma, including inhaler medicaments such as corticosteroids and β2 agonists, have not been shown to have adverse effects on tooth development. They have been shown to decrease plaque pH after administration. However, their association with increased susceptibility or resistance to dental caries has been equivocal, with some studies reporting an increased susceptibility to caries with use of antiasthma medications and others reporting no increased susceptibility.

**TABLE 1.** Effects of Some Chemicals, Drugs, and Physical Agents on Teeth

<table>
<thead>
<tr>
<th>Agent</th>
<th>Stage of Development</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Embryo, infant, child, adolescent, adult</td>
<td>May affect tooth development; may enhance susceptibility to dental caries</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Embryo, infant, child, adolescent, adult</td>
<td>May affect tooth development; ETS may enhance susceptibility to dental caries; enhances susceptibility to dental caries and periodontal disease</td>
</tr>
<tr>
<td>Mercury</td>
<td>Embryo, infant, child, adolescent, adult</td>
<td>No apparent effect on teeth Excess intake during enamel maturation may cause hypomineralization; no adverse effect on mineralization once enamel maturation is complete</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Embryo, infant, child, adolescent, adult</td>
<td>No apparent effect on teeth May affect tooth development; may enhance susceptibility to dental caries</td>
</tr>
<tr>
<td>Dioxins</td>
<td>Embryo, infant, child, adolescent, adult</td>
<td>May affect tooth development; may enhance susceptibility to dental caries</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Embryo, infant, child, adolescent, adult</td>
<td>May cause tooth discoloration; no apparent effect on teeth</td>
</tr>
<tr>
<td>Other drugs</td>
<td>Embryo, infant, child, adolescent, adult</td>
<td>May affect tooth development; may enhance susceptibility to dental caries</td>
</tr>
<tr>
<td>Physical agents (trauma)</td>
<td>Embryo, infant, child, infant, adolescent, adult</td>
<td>May affect tooth development; may result in injury to teeth, soft tissues, and supporting structures</td>
</tr>
</tbody>
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**PHYSICAL AGENTS**

Few physical agents are as damaging to the dentition and craniofacial complex as is trauma. Furthermore, it has been estimated that as many as one third of all dental injuries and up to 19% of injuries to the head and face are sports related. The consequences of sports-related injuries run the gamut, ranging from chipped or fractured teeth (Fig 3) to loss of 1 or more teeth, facial lacerations, contusions, and bone fractures. The majority of these injuries occur in children and adolescents, although protective equipment including helmets, face shields, and mouth guards are mandatory in many sports today. Although use of appropriate head, face, eye, and mouth protection for children and adolescents who participate in school-sponsored physical activities has been encouraged and adopted as a Healthy People 2010 objective, there is, as yet, insufficient evidence that planned interventions have been effective in reducing the prevalence or incidence of sports-related injuries to the mouth and face. Clearly, much remains to be discovered regarding attitude and effective use of protective equipment.

**CONCLUSION**

In this brief review, we have described what is known about the more common environmental chemicals, drugs, and physical agents on teeth dur-
ing various stages of development, from the embryo to the adult (Table 1). As a generalization, teeth are most vulnerable and sensitive to the toxic effects of environmental chemicals and drugs during their development and before eruption into the mouth. The risk of physical injury to teeth and supporting structures must also be considered in children and adolescents. Studies of sports-related injuries in adults are especially applicable to children. Although many questions remain on the prevention and control of sports-related craniofacial injuries, many of the data on safeguards to protect the teeth and craniofacial complex of adults can be extrapolated to children. However, there is a significant need for continued research on more effective methods to educate parents, coaches, health professionals, and children about the dangers of unprotected teeth and sports-related craniofacial injuries.

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# Teeth
Ronald J. Billings, Robert J. Berkowitz and Gene Watson

*Pediatrics* 2004;113;1120

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