Endotoxins and Cancer

Jessica I. Lundin and Harvey Checkoway

Department of Environmental and Occupational Health Sciences, University of Washington School of Public Health, Seattle, Washington, USA

OBJECTIVE: Exposure to endotoxin, a component of gram-negative bacterial cell walls, is widespread in many industrial settings and in the ambient environment. Heavy-exposure environments include livestock farms, cotton textile facilities, and saw mills. Concentrations are highly variable in nonoccupational indoor and outdoor environments. Endotoxin is a potent inflammmogen with recognized health effects, including fever, shunting chills, septic shock, toxic pneumonitis, and respiratory symptoms. Somewhat paradoxically, given the putative role of inflammation in carcinogenesis, various lines of evidence suggest that endotoxin may prevent cancer initiation or limit tumor growth. The hypothesis that components of bacteria may retard cancer progression dates back to William B. Coley’s therapeutic experiments (“bacterial vaccine”) in the 1890s.

DATA SOURCES: In this article, we review epidemiologic, clinical trial, and experimental studies pertinent to the hypothesis that endotoxin prevents cancer. Since the 1970s, epidemiologic studies of cotton textile and other endotoxin-exposed occupational groups have consistently demonstrated reduced lung cancer risks. Experimental animal toxicology research and some limited therapeutic trials in cancer patients offer additional support for an anticarcinogenic potential. The underlying biological mechanisms of anticarcinogenesis are not entirely understood but are thought to involve the recruitment and activation of immune cells and proinflammatory mediators (e.g., tumor necrosis factor α and interleukin-1 and -6).

CONCLUSIONS: In view of the current state of knowledge, it would be premature to recommend endotoxin as a cancer-chemopreventive agent. Nonetheless, further epidemiologic and experimental investigations that can clarify further dose–effect and exposure–timing relations could have substantial public health and basic biomedical benefits.

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Endotoxins are integral components of the outer membrane of gram-negative bacteria cell walls, composed of proteins, lipids, and lipopolysaccharide (LPS), which are released when bacteria lyse (Campbell et al. 2008). LPS is considered to be responsible for most of the biological properties of bacterial endotoxins, particularly the lipid component (lipo A, a phosphoglycolipid) (Hodgson 2006; Reisser et al. 2002). Endotoxins are a contaminant of various organic dusts and other environmental media that support gram-negative bacterial growth [Centers for Disease Control and Prevention (CDC) 2006; Gehring et al. 2004; Liebers et al. 2006; Park et al. 2006]. The bacterial constituents are continuously shed into our surrounding environment; consequently, exposure to endotoxin is extremely widespread.

The Limulus amoebocyte lysate (LAL) assay for environmental endotoxin levels was adopted as the standard assay of endotoxin detection by the U.S. Food and Drug Administration in the 1980s (Liebers et al. 2006). This assay is based on the activation of a clotting enzyme in the lysate. Endotoxin levels are often expressed as endotoxin units (EU; 1 EU = 0.1 ng, depending on the reference standard), or as concentration of endotoxin per milligram of dust or per cubic meter of air. Of note, LAL tests are not internationally standardized, and measurements may vary among laboratories (Liebers et al. 2006).

Of particular interest from a health effects perspective are the more intense exposures experienced in numerous manufacturing and agricultural settings throughout the world. Substantial endotoxin exposure occurs in agricultural work, garbage handling, sewage treatment, and incineration industries, textile industries (particularly cotton products factories), and saw mills, and to a lesser degree in occupations with exposures to certain types of water-based metalworking fluids and in cigarette factories, fiberglass production facilities, and paper mills, among others (Astrandriakikas et al. 2007; CDC 1998; Kuzmickiene et al. 2004; Liebers et al. 2006; Mandryk et al. 1999; Nieuwenhuijzen et al. 1999; Rapiti et al. 1997). Cotton factories in the Shanghai textile industry have been documented to have high endotoxin exposure concentrations (Astrandriakikas et al. 2007). By way of illustration, the mean of the endotoxin levels that have been measured in representative cotton factories was 366 EU/m³ (range, 44–1,871 EU/m³) (Astrandriakikas et al. 2006a). Additionally, reported mean endotoxin concentrations of 40 and 48 EU/m³ have been reported among municipal waste management workers (Spaan et al. 2006; Wouters et al. 2006). In the agricultural industry, an overall mean endotoxin concentration of 230 EU/m³ has been reported, with mean measurements of 2,700 EU/m³ (range, 96–42,300 EU/m³) in the grain, seeds, and legume primary production sector and 1,190 EU/m³ (range, 62–8,120 EU/m³) in the primary animal production sector (Spaan et al. 2006). Other studies have reported endotoxin levels for livestock farmers ranging from 11 to 159 EU/m³ and field crop and fruit farming exposure levels ranging from low to >1,500 EU/m³ (Nieuwenhuijzen et al. 1999), and an exposure concentration of 140 EU/m³ among swine farmers (Chang et al. 2001).

Endotoxin is ubiquitous in the environment, although the exposure in occupational settings, frequently >100 ng/m³, is more intense than exposure in the home, < 1 ng/m³ (Rylander et al. 1989). Nonetheless, adverse health effects have been observed at endotoxin levels as low as 0.2 ng/m³ (Smid et al. 1992). The human health effects of acute exposure to endotoxin include sepsis; clinical symptoms such as fever, shaking chills, and septic shock; and, at lower doses, toxic pneumonitis, lung function decrements, and respiratory symptoms, such as byssinosis (“Monday morning chest tightness”) (Rylander 2002, 2006). Chronic exposures have been related to the risk of developing nonatopic chronic obstructive pulmonary diseases (Schwartz et al. 1995; Smid et al. 1992; Wang et al. 2005) and to the severity of asthma (Michel et al. 1996). In contrast, numerous studies have demonstrated seemingly protective effects of environmental endotoxin exposure on atopic asthma risk and allergy development in early childhood (Remes et al. 2003; von Mutius et al. 2000), and atopy in adults (Edvard et al. 2004; Gehring et al. 2004; Portengen et al. 2005). As we discuss in some detail in this article, an inverse association with endotoxin exposure and the risk of cancer of the lung, and potentially other cancer end points, has consistently been demonstrated.

More than a century of clinical, laboratory, and epidemiologic research demonstrates that...
Endotoxin has antitumor properties (Liebers et al. 2008; Liu 2002), but an understanding of the underlying mechanisms, and the subsequent development of an effective therapeutic application of endotoxin, has yet to be elucidated. We reviewed current and historical literature identified in Medline (National Library of Medicine 2006) electronic database, 1973–2008, using combinations of search key words such as endotoxin, LPS, epidemiology, lung, cancer, farmer, textile, and cotton. The text and citations of all identified supporting articles were reviewed with a particular focus on lung cancer, cotton textile workers [studies of textile workers that did not specify type of textile (i.e., cotton) were not reviewed], and studies of farmers by type of farming (dairy, crop, etc.). In addition a Medline search of publications from 1990 to 2008 was performed that reviewed the underlying mechanism of action so as to best describe the paradoxical understanding and association of the immune system response to endotoxin exposure and cancer.

In this review we discuss the historical and current understanding of the association of endotoxin exposure and cancer, therapeutic uses/treatment of cancer with LPS, epidemiologic studies of endotoxin exposure, and the underlying mechanisms to explain the human studies.

Endotoxin and Cancer

Early experiments. In the late 19th century, William B. Coley, with the assistance of established anecdotal theories of the beneficial effect of fever on tumors (McCarthy 2006), recognized regression and, in some cases, necrosis of tumors in advanced cancer patients suffering concomitant bacterial infections. Coley went on to successfully treat cancer in terminally ill patients by injecting mixed bacterial toxins in and around the tumors (Coley 1894). Despite the successes, this treatment was discontinued because the anticancer effect in patients was not consistent and repeated injections caused severe side effects, such as high fever and chills, that were not yet understood (Mueller 1998). In the early 1940s, LPS was identified as the active ingredient in Coley’s “bacterial vaccine,” and the antitumor effects of the bacterial polysaccharide were successfully demonstrated in vivo (Shear and Perrault 1944; Shear and Turner 1943). When isolated LPS was found to be ineffective as an antitumor agent in culture, it was determined that the effects were mediated by host-dependent mechanisms. Almost three decades later, tumor necrosis factor α (TNF-α) was determined to be the effective agent with antitumor properties (Carswell et al. 1975). By the mid-1980s therapeutic uses of TNF-α were being tested, but the therapy was less effective than hoped and caused undesired side effects, such as headache, nausea, vomiting, fever, hypotension, and diarrhea (Clark 2007; Mueller 1998; Spriggs et al. 1988). Around the same time, it was discovered that TNF-α was identical to cachectin, a mediator responsible for cachexia associated with sepsis (Clark 2007; Ghезzi and Cerami 2005). The adverse effects of TNF-α were quickly accepted as limitations to its direct use as an antitumor agent (Ghезzi and Cerami 2005; Mueller 1998).

Treatment of cancer with LPS. Laboratory studies have successfully demonstrated therapeutic effects when administering LPS, or synthetic lipid A molecule, including inhibition of tumor size and growth (Andreani et al. 2007; Chicoine et al. 2001; Kuramitsu et al. 1997; Morita et al. 1996). Morita et al. (1996) demonstrated this effect to be dose dependent. Additionally, an increased survival time has been noted for mice infected with cancer cells that have been inoculated with LPS (Andreani et al. 2007; Lange 1992). An inverse dose–response association was demonstrated on the survival of cancer-bearing rats that were administered a synthetic analogue of lipid A (Kuramitsu et al. 1997). Furthermore, antitumor memory has been demonstrated on mice with tumor cells planted intracranially; the mice with previous LPS-eradicated tumors showed increased survival compared with those without previous tumors (Won et al. 2003).

Subsequently small clinical trials administering LPS, or a lipid A analog, have been performed. Cancer remission and disease stabilization have been demonstrated in cancer patients (de Bono et al. 2000; Engelhardt et al. 1991; Goto et al. 1996; Otto et al. 1996). However, clinical toxicities have been unavoidable, even with the pretreatment of ibuprofen (de Bono et al. 2000; Engelhardt et al. 1991; Otto et al. 1996).

Epidemiologic studies of endotoxin exposure and cancer risk. Lung cancer. Cancer risks, particularly lung cancer, have been investigated in relation to occupational endotoxin exposures (Table 1). Cotton textile and farming industries have been a particular focus of epidemiologic research because of the substantial endotoxin exposure in these occupational settings, so we review these two industries in detail. Findings from early occupational cohort studies demonstrated reduced risks for lung cancer among cotton textile workers in the United States (Henderson and Enterline 1973; Merchant and Ortmeyer 1981) and the United Kingdom (Hodgson and Jones 1990), particularly in those with longer durations of employment. These results were regarded as somewhat surprising when first observed. Lower than expected lung cancer risks were subsequently reported from a cohort study conducted among women textile workers in Shanghai (Astrakianakis et al. 2007; Wernli et al. 2003), a separate, unrelated, case–control study of both men and women in the cotton textile industry in Shanghai (Levin et al. 1987), cotton textile workers in Poland (Szeszenia-Dabrowska et al. 1999), and a study of Italian cotton mill workers (Mastrandelo et al. 2008). Slightly elevated lung cancer risks were noted in Lithuanian and Finnish cohorts of cotton textile workers (Koskela et al. 1990; Kuzmickiene et al. 2004); however, extended follow-up of...
the Lithuanian cohort, by 5 years, indicated significantly reduced lung cancer risk among male workers employed for at least 10 years (Kuzmickiene and Stukonis 2007), and the reported risk in the Finnish cohort was based on three cases. In a meta-analysis of studies of cotton workers published during or before 1990, and of studies published during or before 2002, lung cancer risk was significantly reduced (Mastrangelo et al. 2002). Of note, the risk estimate for lung cancer was closer to unity when the more recent studies were included. The authors of the meta-analysis hypothesized this may be due to a lowering of dust concentration in the workplace in recent years.

Protection for lung cancer has been demonstrated to be similar among different types of farming (Blair et al. 2005; Lee et al. 2002), although most studies reviewed demonstrated a greater protective effect in livestock farmers, specifically dairy farmers, compared with orchard/crop farmers (Laakkonen and Punkala 2003; Lange et al. 2003; Mastrangelo et al. 1996, 2004; Punkala and Novotka 1997; Reif et al. 1989; Lange et al. 2003) demonstrated that the risk difference was statistically significant. Additionally, crop farmer exposures are predominantly during warmer harvest months (3–4 months) and may not be representative of the actual annual dose, whereas the exposure experience of livestock farmers occurs 12 months a year (Lange et al. 2003; Nieuwenhuijsen et al. 1999; Spaan et al. 2006). For these reasons, and for simplification of discussion by selecting a homogeneous population, studies of dairy farmers are the focus of this review.

Inverse associations with respiratory cancers have consistently been observed among dairy farmers (Laakkonen and Punkala 2008; Mastrangelo et al. 2004, 2005; Punkala and Novotka 1997; Reif et al. 1989; Stark et al. 1990; Wang et al. 2002) (Table 1). In a cohort of Italian dairy farmers, an inverse association with increased number of dairy cattle on the farm was demonstrated; a significant inverse trend (p = 0.001) was reported for farmers with more recent exposures (Mastrangelo et al. 2004, 2005). Lung and bronchus cancer risks were significantly lower among Finnish dairy farmers who continued farming at the time of follow-up (20-year lag time) than for those that had quit farming, and risk of lung cancer was elevated for farmers who changed their production type to a crop or to beef cattle from the beginning of the study to follow-up, compared with those who continued as dairy farmers (Laakkonen and Punkala 2008). An earlier follow-up from this same Finnish Farm Register base cohort also demonstrated a significant decrease in lung and bronchus cancer mortalities among dairy farmers and reported the risk was lowest among farmers with at least 10 dairy cows (Punkala and Nortkola 1997).

Lung cancer mortality and incidence has also been shown to be significantly reduced in livestock farmers in the U.S. and Iceland, respectively (Gunnarsdottir and Rafnsson 1991; Lange et al. 2003).

Only limited epidemiologic evidence is available from investigations of lung cancer risks in nontextile and nonfarming occupations that entail endotoxin exposure, yet the findings are generally consistent with an anticarcinogenic effect. Reduced lung cancer risks have been observed in U.S. automotive workers exposed to endotoxin from water-based metalworking fluids (Schroeder et al. 1997). The associations were primarily attributable to exposures within 10 years of death. Markedly reduced lung cancer incidence was also observed among pesticide applicators in the Agricultural Health Study cohort in the United States, which was attributed to a low prevalence of smoking habits (Alavanja et al. 2004; Blair et al. 2005). Pesticides were the principal focus of that study; endotoxin has not yet been investigated as a possible explanatory factor for the lung cancer deficit. A deficit in lung cancer risk was also observed in a study of more than a million Finnish men based on their self-reported longest held occupation in the 1970 national census, lagged by 20 years, with endotoxin exposure determined by an occupational exposure matrix (Laakkonen et al. 2008): a deficit was not observed in women. In contrast, a study of occupational exposures in Leningrad Province, Russia, reported a >2-fold greater risk of lung cancer in subjects ever occupationally exposed to cotton dust (Baccarelli et al. 2006). Of note, the risk estimate was based on six cases, and the evaluation of cumulative exposure to cotton dust in males resulted in a protective effect.

Among the studies of endotoxin exposure and lung cancer, quantitative estimates of historical endotoxin exposures have been reconstructed for the Lithuanian (Kuzmickiene and Stukonis 2007) and Shanghai (Astrakianakis et al. 2006b, 2007) cohorts, and qualitative estimates of exposure have been estimated for Italian dairy farmers (Mastrangelo et al. 2005), to enable dose–response estimations of numerous site-specific cancers. All cohorts demonstrated a significant inverse dose response trend when evaluating endotoxin exposure by dust exposure category, cumulative cotton dust exposure, and number of dairy cattle on the farm, respectively, and lung cancer.

Other cancers. The findings to date for endotoxin exposure and risks for malignancies other than lung cancer have been limited and inconsistent. Much of the risk information on industrial exposures has been derived from the Shanghai cohort study of female textile workers. The first publication of this cohort described the occupational cancer risk for all textile workers, with select cancer outcomes evaluated by textile sector (Wernli et al. 2003). A decreased risk of most cancers was reported, with a significant decrease for esophageal, stomach, rectal, cervical, ovarian, and bladder cancers. Subsequent publications of this cohort evaluated the association of cumulative quantitative endotoxin exposure, as well as duration of occupational exposure classified by a job exposure matrix, and individual cancer end points, including liver, esophagus, stomach, rectum, pancreas, breast, brain, ovary, nasopharynx, and thyroid (Chang et al. 2006; De Roos et al. 2003; Gold et al. 2006; Li et al. 2006a, 2006b; Ray et al. 2007; Wernli et al. 2006, 2008; Wong et al. 2006). Notable findings from these studies include a decreased risk for cancer of the esophagus [hazard ratio (HR) = 0.5; 95% confidence interval (CI), 0.2–1.1] and increased risk for cancer of the nasopharynx (HR > 2.5; 95% CI, 1.1–5.4) (Li et al. 2006b; Wernli et al. 2006).

Other cotton textile industry cohorts have been evaluated for the association of occupational endotoxin exposure and cancers other than the lung. Szeszenia-Dabrowska (1999) reported a decreased risk of digestive cancers for men and women working in spinning and weaving departments. When considering individual cancers in men, there was a suggested increased risk of colon and liver cancers in weavers and stomach cancer in spinners, although these individual assessments were based on small numbers. Individual cancers in women showed a suggested decrease risk of rectal/anal and liver cancers and a suggested increase in gallbladder and ovarian cancers. In a Lithuanian cohort of textile workers, female workers in the spinning and weaving departments demonstrated increased risks for most individual cancers evaluated, with significant findings for breast and cervical cancers (Kuzmickiene et al. 2004). Other studies of cotton textile factory cohorts that defined exposure as employment in the production facility reported a decrease in breast and digestive cancers (Henderson and Enterline 1973; Hodgson and Jones 1990) and an increase in bladder, pharyngeal, and digestive cancers (Henderson and Enterline 1973; Mastrangelo et al. 2008). In a meta-analysis of 15 studies of cotton workers published during or before 1990, a nonsignificant increased risk of bladder cancer and decreased risk of digestive cancer were reported (Mastrangelo et al. 2002).

Among Finnish dairy farmers that continued farming at the time of follow-up (20-year lag time), the risks of colon, liver, breast, bladder, and skin cancers were significantly decreased, and risk of lip cancer was significantly increased (Laakkonen and Punkala 2008). Mastrangelo (2005) reported a decreased risk of mortality associated with most cancers evaluated in a cohort of Italian dairy farmers, with a significant decrease in
esophageal, pancreatic, and bladder cancers. In a cohort of predominantly dairy farmers, female and male, in New York State, a decrease in risk was reported for most cancers, with significant decreases in risk for colon/rectum and ovarian cancers in females and cancers of the oral cavity, large intestine, and bladder in males (Stark et al. 1990; Wang et al. 2002).

**Physiologic response to endotoxin exposure and cancer risk.** Various mechanistic arguments have been advanced regarding endotoxin and carcinogenesis, focusing largely on complex interactions between the innate and adaptive immune systems (Schmidt 2006; Tzianabos and Wetzler 2004). Once internalized, LPS is bound by LPS-binding protein (LBP) and then transferred to CD14 protein (Figure 1). The CD14–LPS complex binds to and activates the Toll-like receptors (TLRs), which are cell membrane signaling proteins located on cell surfaces of macrophages and other cells. TLR4 is the predominant receptor for endotoxin and is required for endotoxin recognition (Poltorak et al. 1998). Upon recognition of LPS, the innate inflammatory response is initiated and proinflammatory cytokines are released, including TNF-α, interleukin (IL)-1, and IL-6, which recruit immune cells to the site of exposure and induce the acute-phase response (Reiser et al. 2002; Tzianabos and Wetzler 2004). This host response is important for an effective immune system; however, overproduction of proinflammatory factors can cause endotoxic shock. In addition, TLR activation induces the expression of CD80 and CD86 on the surface of antigen-presenting cells that interact with the adaptive immune system to activate naïve T-lymphocyte cells (T cells) (Heine et al. 2001; Hodgson 2006; Werling and Jungi 2003). The maturation of helper T cells (Th1) results in cell-mediated (Th1)1 and humoral (Th1)2 subpopulations. The cytokines released by each of these cells have unique profiles and suppress the proliferation of the other subpopulation (Tzianabos and Wetzler 2004). The immune reaction to LPS primarily activates Th1 cells, which maximize the killing efficiency of macrophages and induce up-regulation of proinflammatory mediators (Heine et al. 2001; Laptev et al. 2000; Werling and Jungi 2003). Notably, antitumor activity has been related to the cytokine profile associated with a Th1 response, whereas the Th1,2 profile has been shown to be ineffective in eradicating tumors (Hong et al. 2008; Maraveyas et al. 1999).

**Lung cancer.** It has been postulated that bacterial endotoxin, through immunologic mechanisms, can be protective against lung cancer. Insofar as the route of endotoxin exposure is predominantly inhalation, the lung is one of the initial sites of immune stimulation (Liebers et al. 2006). Additionally, Klein et al. (1994) showed in a rat model that 5 min after injection of *Escherichia coli*, the 20% of bacteria not taken up by the liver were found in the lungs, spleen, and blood. The Th1 response favored by LPS-activated immune cells may be a conjectured benefit to this initial site of exposure in that the Th1 immune response tends to be more localized than the Th1,2 response (Tzianabos and Wetzler 2004). Moreover, the lung has been shown to produce or up-regulate the production of cofactors involved in the host response, including LBP, CD14, and TLR4, after LPS exposure (Fears et al. 1995; Matsumura et al. 2000; Su et al. 1994). It is generally accepted that LBP is produced in the liver, but it has been shown that significant levels of LBP could be produced elsewhere in the body under induced conditions, such as an inflammatory response (Su et al. 1994). In the presence of LBP, approximately 15-fold less LPS have been reported to be required to trigger an inflammatory response, as measured using TNF-α (Martin et al. 1992; Schumann et al. 1990). There is also consistent experimental evidence for an increase in TNF in the bronchoalveolar lavage (BAL) fluid in guinea pigs after cotton dust exposure (Ryan and Karol 1991), and an increase in TNF in the BAL fluid of humans after endotoxin exposure (Jagielo et al. 1996; O'Grady et al. 2001; Wang et al. 1997). Likewise, Michel et al. (1997) reported a dose-dependent increase in TNF in the spurt of LPS-exposed subjects.

**Other cancers.** Other cancer end points have been studied, including cancers of the liver, esophagus, stomach, rectum, pancreas, breast, brain, ovary, thyroid, and nasopharynx, but not as extensively as the lung, and the findings have been inconsistent (Chang et al. 2006; De Roos et al. 2005; Gold et al. 2006; Henderson and Enterline 1973; Hodgson and Jones 1990; Kuzmickiene et al. 2004; Laakonen et al. 2008; Li et al. 2006a; Mastrandelo et al. 2008; Merchant and Ortmeyer 1981; Ray et al. 2007; Stark et al. 1990; Sznesia-Dabrowska et al. 1999; Wang et al. 2002; Wernli et al. 2003, 2006, 2008; Wong et al. 2006). Nonetheless, subsequent effects in other organ systems are plausible because cells with TLR4 receptors are widely disseminated, and elevation of systemic inflammatory mediators, including TNF-α, IL-1, IL-6, and IL-8, has been shown after inhalation of LPS or media contaminated with endotoxin (Hodgson 2006; Larsson et al. 1994; Mackensen et al. 1992; Matsuys and Rylander 1978; Michel et al. 1997; Palmberg et al. 2002; Reiser et al. 2002). Additionally, a dose-related systemic response to inhaled LPS in human subjects after bronchial challenges with pure LPS has been demonstrated (Michel et al. 1997).

**Discussion: Future Research Needs**

The individual immune response to endotoxin is a complicated result of dose, timing, potential additive or synergistic effects, and genetically determined responsiveness (Liebers et al. 2008). The health effects, including cancer outcomes associated with exposure, remain paradoxical.

**Underlying biological mechanisms need to be elucidated.** Insofar as endotoxin provokes an inflammatory response (Gordon 1992; Larsson et al. 1994; Matsuys and Rylander 1978; Michel et al. 1997), it might reasonably be anticipated that inflammation would enhance, rather than prevent, carcinogenesis (Bohnhorst et al. 2006; Puntoni et al. 2008; Schottenfeld and Beebe-Dimmer 2006). A sizable proportion of cancer deaths has been postulated to be attributable to infectious agents in which inflammation, mediated by recruitment of cytokines and growth factors to infected sites, may influence susceptibility to carcinogenesis through DNA damage and the simultaneous promotion of tissue destruction and repair (Schottenfeld and Beebe-Dimmer 2006). The roles of *H. pylori* (which generates endotoxin) in the etiology of adenocarcinoma of the stomach, human papillomavirus in the
etiology of anogenital carcinoma, and hepatitis B or C virus in hepatocellular carcinoma are cases in point (Britton et al. 2005; Schottenfeld and Beebe-Dimmer 2006). Additionally, over-stimulation of inflammatory responses can lead to severe clinical symptoms, often termed sepsis, which can lead to progressive organ failure and death (Boshart and Heinzelmann 2007). However, in lesser doses, which may relate best to chronic low-dose occupational and environmental endotoxin exposure, the proinflammatory mediators have been shown to inhibit tumor growth and retard tumor progression (Carswell et al. 1975; Dranoff 2004; Lin and Karin 2007; Manda et al. 1987).

Exposure to LPS has been demonstrated to induce pathologic hyperactivity (Suter and Kirsanow 1961), but a mechanism of protection from this lethality, termed endotoxin tolerance, has been speculated. Endotoxin tolerance is the unresolved phenomenon defined as an altered capacity to respond to LPS activation immediately after a first exposure; that is, when exposed to continual small doses of LPS, the same TNF response of the initial exposure does not necessarily occur with subsequent exposure (Cross 2002; Engelhardt et al. 1991; Gioannini et al. 2003; Michel et al. 1997; Otto et al. 1996; Palmberg et al. 2002). This tolerance has been shown to vary as dose by as well as by length of time between treatments, and is theorized to allow the host more time to rid the pathogen (Cross 2002; Engelhardt et al. 1991). Because this tolerance has been related to allowing a body system to endure continuous small doses without adverse symptoms, a better understanding of this mechanism may bring clarity to the relationships between endotoxin sensitivity (including acute toxic effects) and sepsis, and, possibly, between carcinogenesis and protection against cancer (Cross 2002).

Epidemiologic corroboration. Experimental evidence from both animal models and therapeutic trials regarding the effects of endotoxin on carcinogenic processes has not been consistent (Chen et al. 2007; Mumford and Otten 2008), which indicates the importance of epidemiologic observations for guiding mechanistic and clinical research. Difficulties in studying endotoxin epidemiologically include the very large degree of exposure variability over time and among study subjects, and uncertainties in the measurement, or proxy measure, of exposure (Spaan et al. 2008). The general pattern of endotoxin exposure and cancer that emerges from existing epidemiologic research is one suggestive of an anticarcinogenic effect of endotoxin exposure that occurs in the lung and, perhaps, other organs. This consistency of findings has been maintained when using job history as a proxy of exposure (Henderson and Enterline 1973; Hodgson and Jones 1990; Kuzmickiene and Stukonis 2007; Laakkonen and Pukkala 2008; Lange et al. 2003; Mastrangelo et al. 2008; Merchant and Ortmeyer 1981; Stark et al. 1990; Wang et al. 2002; Wernli et al. 2003), incorporating a cumulative endotoxin exposure matrix variable (Astrakianakis et al. 2007; Kuzmickiene and Stukonis 2007; Schroeter et al. 1997), and using number of dairy cattle on the farm (Mastrangelo et al. 2005). Nonetheless, with a few exceptions, most epidemiologic studies of endotoxin and cancer have not incorporated quantitative estimates of endotoxin exposure, which would strengthen causal arguments.

Although not unique to epidemiologic studies of endotoxin and cancer, absence of data on potentially confounding factors has been a limitation of most studies to date. Smoking status was incorporated in select analyses of endotoxin exposure and cancer and was shown not to account for the whole reduction in lung cancer risk, although the effect was exaggerated in those with low smoking habits (Astrakianakis et al. 2007; Blair et al. 2005; Hodzon and Jones 1990; Lange et al. 2003; Mastrangelo et al. 2004, 2005). Specifically, in the study of lung cancer among Shanghai textile workers, the inverse dose–response relation was not confounded by smoking, and importantly, the apparent protective effect was seen among both smokers and nonsmokers (Astrakianakis et al. 2007). The very low prevalence of smoking in this cohort of Chinese women workers precludes generalizability of these observations (Wernli et al. 2003), thus underscoring the importance of obtaining pertinent data on smoking and other cancer risk factors in future research.

Concluding Remarks
Exposure to endotoxin is ubiquitous in the environment at levels that have been shown to have physiologic effects and, in some instances, demonstrable health consequences. There is very consistent epidemiologic evidence that endotoxin is dose-related to risk reductions for lung cancer, and provocative evidence that risks for other cancers may be similarly reduced. Animal experimental research and limited therapeutic trial data are generally supportive of an anticarcinogenic effect, and plausible biological mechanisms have been described. The public health implications of findings to date could be substantial. Nevertheless, a more extensive assessment of the role of endotoxin in the etiology of cancers of the lung and other organs is needed. Future epidemiologic and toxicologic research to elucidate more precisely dose–response relations and underlying mechanisms will need to be conducted before endotoxin, an agent with established noncancer toxic health effects, could be considered for widespread chemoprevention uses (Boffetta et al. 2007).

REFERENCES
Alavanja MC, Dosemeci M, Samanic C, Lubin J, Lynch CF, Knott C, et al. 2004. Pesticides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol 160(9):876–885.
Andrani V, Gatti D, Simionella L, Rivero V, Maccioni M. 2007. Activation of Toll-like receptor 4 on tumor cells in vitro inhibits subsequent tumor growth in vivo. Cancer Res 67(21):10519–10527.
Astrakianakis G, Seixas NS, Camp J, Smith TJ, Bartlett K, Checkoway H. 2006a. Cotton dust levels in three Shanghai textile factories: a comparison of samplers. J Occup Environ Hygiene 3(8):418–427.
Astrakianakis G, Seixas NS, Camp JE, Christiani DC, Feng Z, Thomas DB, et al. 2006b. Modeling, estimation and validation of cotton dust and endotoxin exposures in Chinese textile operations. Ann Occup Hyg 50(6):573–582.
Astrakianakis G, Seixas NS, Ray R, Camp JE, Gao DL, Feng Z, et al. 2007. Lung cancer risk among textile workers exposed to endotoxin. J Natl Cancer Inst 99(5):357–364.
Baccarini A, Kimmelstiltski O, Tretiakova M, Gorbanas S, Lomteva A, Klimkina I, et al. 2006. Risk of lung cancer from exposure to dusts and fibers in Leningrad Province, Russia. J Ind Med 49(8):160–167.
Blair A, Sandler DP, Tarone R, Lubin J, Thomas K, Hoppin JA, et al. 2005. Mortality among participants in the agricultural health study. Ann Epidemiol 15(4):279–285.
Boffetta P. 2007. Endotoxins in lung cancer prevention. J Natl Cancer Inst 99(5):339.
Böhnhorst J, Rasmussen T, Moen SN, Flottum M, Knudsen L, Borset M, et al. 2006. Toll-like receptors mediate proliferation and survival of multiple myeloma cells. Leukemia 20(6):1138–1144.
Boshart H, Heinzelmann M. 2007. Targeting bacterial endo-toxin: two sides of a coin. Ann N Y Acad Sci 1096:1–17.
Britton S, Pappo-Szabo E, Simula-Grant J, Morrison L, Taylor DE, Monteiro MA. 2005. A novel Helicobacter pylori cell-surface polysaccharide. Carbohydr Res 340(9):1605–1611.
Campbell NA, Reece JB, Ury LA, Cain ML, Wasserman SA, Minorsky PV, et al. 2008. Biology. 8th ed. San Francisco, CA: Benjamin Cummings.
Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. 1975. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA 72(6):366–370.
CDC. 1998. What You Need to Know about Occupational Exposure to Metalworking Fluids. DHHS (NIOSH) Publication No. 98–116. Atlanta, GA:Centers for Disease Control and Prevention.
CDC (Centers for Disease Control and Prevention). 2006. Health concerns associated with mold in water-damaged homes after hurricanes Katrina and Rita—New Orleans area, Louisiana, October 2005. MMWR Morb Mortal Wkly Rep 55(2):41–44.
Chang CK, Astrakianakis G, Thomas DB, Seixas NS, Ray RM, Gao DL, et al. 2006. Occupational exposures and risks of liver cancer among Shanghai textile workers—a case–cohort study. Int J Epidemiol 35(2):361–369.
Chang CW, Chung H, Huang CF, Su HJ. 2001. Exposure assessment to airborne endotoxin, dust, ammonia, hydrogen sulfide and carbon dioxide in open style swine houses. Ann Occup Hygiene 45(6):457–465.
Chen R, Alvero AB, Silasi DA, Mor G. 2007. Inflammation, cancer and chemoresistance: taking advantage of the Toll-like receptor signaling pathway. Am J Reprod Immunol 57(2):93–107.
Chicoine MR, Won EK, Zahner MC. 2001. Intratumoral injection of lipopolysaccharide causes regression of subcutaneously implanted mouse glioblastoma multiforme. Neurosurgery 48(3):607–615.
Clark IA. 2007. How TNF was recognized as a key mechanism of disease. Cytokine Growth Factor Rev 18(3):335–343.
Coley WB. 1894. Treatment of inoperable malignant tumors with the toxins of erysipelas and the bacillus prodigiosus. Trans Am Surg Assn (12):183–212.
Cross AS. 2002. Endotoxin tolerance–current concepts in historical perspective. J Endotoxin Res 8(3):93–98.
de Boer J, Dalgalush AD, Carman-Gram J, Diefley J, Lofs FJ, Dyke F, et al. 2000. Phase I study of ONO-4007, a synthetic analogue of the lipid A moiety of bacterial lipopolysaccharide. Clin Cancer Res 6(2):397–405.
De Roos AJ, Ray RM, Gao DL, Feng Z, Egan KD, Fiblings ED, Ziding F, et al. 2005. Colorectal cancer incidence among female textile workers in Shanghai, China: a case–control analysis of occupational exposures. Cancer Causes Control 16(10):1177–1188.
Lapa e Silva JR, Possebon da Silva MD, Lefort J, Vargaftig BB. 1995. Phase I trial of intravenously administered endotoxin (Salmonella abortus equi) in cancer patients. Cancer Res 55(10):2254–2530.

Fearn C, Kravchenko VV, Ulevitch RJ, Loskutoff DJ. 1995. Macrophage gene activation in vivo: extramitochondrial synthesis and regulation by lipopolysaccharide. J Exp Med 181(5):867–886.

Gehring U, Bischof W, Schleifgott VI, Richter K, Fahlschub W, Wichmann HE, et al. 2004. Exposure to house dust endotoxin and risk of asthma in adults. Allergy 59(8):845–852.

Ghezzi P, Cerami A. 2005. Tumor necrosis factor as a pharmacological target. Mol Biotechnol 31(3):229–244.

Gioannini TL, Teghander A, Zarember KA, Weiss JP. 2002. Regulation of interactions of endotoxin with host cells. J Endotoxin Res 9(6):401–408.

Gold LS, De Roos AJ, Ray RM, Wernli K, Fitzgbibbons ED, Gao DL, et al. 2006. Brain tumors and occupational exposures in a cohort of female textile workers in Shanghai, China. J Occup Environ Health Med 23(3):178–184.

Gordon T. 1992. Dose-dependent pulmonary effects of inhaled endotoxin in guinea pigs. Environ Res 59(2):416–425.

Goto S, Sakai S, Kera J, Suma Y, Soma GI, Takeuchi S. 1996. Cytokine production in human endotoxin-exposed rat hepatoma cells. J Immunol 156(2):551–575.

Gunnarsson M, Raffsonn V. 1991. Cancer incidence among Icelandic farmers 1977–1987. Scand J Soc Med 19(3):173–178.

Heine H, Rietschel ET, Ulmer AJ. 2001. The biology of endotoxin. Microbes Infect 3(1):121–127.

Henderson V, Enterline PE. 1973. An unusual mortality experience in a cohort of female textile workers in Shanghai, China. J Occup Environ Health Med 23(3):178–184.

Lange JH. 1992. An experimental study of anti-cancer properties of tumor necrosis factor. Cancer Immunol Immunother 35(2):115–117.

Lavrijsen P, Bruning T, Raufl-Heimsoth M. 2006. Occupational endotoxin-exposure and possible health effects on humans. Am J Ind Med 49(6):474–481.

Lavrijsen P, Raufl-Heimsoth M, Bruning T. 2008. Health effects due to endotoxin inhalation Arch Toxicol 82(4):203–210.

Lin WW, Karin M. 2007. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 117(5):1175–1183.

Liu AH. 2002. Endotoxin exposure in allergy and asthma: re-considering a paradox. J Allergy Clin Immunol 109(3):379–392.

Mackensen A, Galanos C, Wehr U, Engelhardt R. 1992. Endotoxin tolerance: regulation of cytokine production and cellular functions by repeated application in cancer patients. Eur J Immunol 22(1):571–579.

Manda T, Shimomura K, Mukamoto S, Kobayashi K, Mizota T, Hidir D, et al. 1987. Recombinant human tumor necrosis factor-alpha: evidence of an indirect mode of antitumor activity. Cancer Res 47(14):3707–3711.

Mandryk K, Alwis KU, Hocking AD. 1999. Work-related symptoms and dose-response relationships for personal exposures to dust and endotoxin among woodworkers. Am J Ind Med 35(5):481–490.

Maraveyas A, Baban B, Kennard D, Rook GA, Westby M, Stoehr J, et al. 2002. Defective LPS signaling and TLR4 mutations in patients with atopic dermatitis. J Immunol 169(11):6341–6347.

Murata T, Tsuchida K, Takahashi S, Hasegawa M, Hasegawa H, Ohtsuki F, et al. 2004. Cytokines in lung cancer: clinical and molecular insights. J Thorac Oncol 9(11):1284–1292.

Mumm JB, Oft M. 2008. Cytokine-based transformation of bone and soft-tissue sarcomas. Iowa Orthop J 28:154–158.

Nakamura K, Katsuki H, Ito Y, Ogawa S, Nakamura T, Yamaoka Y, et al. 2004. Mutations in the TLR4 gene are associated with endotoxin hypersensitivity. J Immunol 173(8):4874–4881.

Nair S, Merchant JA, Ortmeyer C. 1981. Mortality of employees of two Florida tire plants. Am J Ind Med 2:121–127.

Nishibe M, Ohiro Y, Matsushita K, Yuan L, Obara T, Fujii A, et al. 2006. Endotoxin and cancer in patients with colorectal and non-small cell lung cancer. Eur J Cancer Sci 321(10):1712–1718.

Olenchock S, Michel O, Kips J, Duchateau J, Vertongen F, Robert L, Collet H, et al. 2006. Personal exposure to dust, endotoxin and crystalline silica in California agriculture. Ann Occup Hygiene 43(1):35–42.

Ollinger EP, Spies HS, Pugin J, Fiuz A, Trapea M, Reles N, et al. 2001. Local inflammatory responses following bran- chial endotoxin instillation in humans. Am J Respir Crit Care Med 163(7):1591–1598.

Ott F, Schmid P, Mackensen A, Wehr U, Seiz A, Braun M, et al. 1999. II. Trial of inhaled endotoxin in patients with colorectal and non-small cell lung cancer. Eur J Cancer Sci 30(1):1712–1718.

Palmberg L, Larssson BM, Malmberg P, Larsson K. 2002. Airway responses of healthy farmers and nonfarmers to exposure in a swine confinement building. Scand J Work Environ Health 28(4):256–263.

Park JH, Cox-Ganss J, Rao C, Kreisel F. 2006. Fungal and endo- toxin measurements in dust associated with respiratory symptoms in a water-damaged office building. Indoor Air 16(3):192–203.

Poltaruk A, He X, Smimouina I, Liu MY, Van Huffel C, Du X, et al. 2008. Defective LPS signaling and TLR4 mutations in lung cancer. Eur J Cancer Sci 44(6):1025–1032.

Portengen L, Preller T, Tielen M, Doekes G, Heederik D. 2005. Endotoxin exposure and atopic sensitization in adult pig farmers. J Allergy Clin Immunol 115(4):797–802.

Pukkala E, Toikka V. Cancer incidence among Finnish farmers, 1979–93. 1997. Cancer Causes Control 8(1):25–33.

Puntoni M, Marra D, Zanardi D, Secchi E. 2008. Inflammation and cancer prevention. Ann Oncol 19(suppl 1):vi225–vi229.

Rapiti E, Sperati A, Fano V, Dell’Oro V, Forastiere F. 1997. Mortality among workers at municipal waste incinerators in Rome: a retrospective cohort study. Am J Ind Med 30(4):391–399.

Reisser D, Pance A, Jeannin JF. 2002. Mechanisms of the anti- tumoral effect of lipid A. Bioessays 24(3):284–289.

Remes ST, Iivanainen K, Koskela H, Pekkanen J. 2003. Which factors explain the lower prevalence of atopy among farmers’ children? Clin Exp Allergy 33(4):427–434.

Ryu KN, Karol MH. 1991. Release of tumor necrosis factor in guinea pigs upon acute inhalation of cotton dust. Am J Resp Cell Mol Biol 5(1):93–98.

Rylander R. 2002. Endotoxin in the environment—exposure and effects. J Endotoxin Res 8(4):241–252.

Rylander R. 2006. Endotoxin and respiratory and cardiovascular disease. Curr Opin Allergy Clin Immunal 6(1):82–66.

Rylander R, Sorensen S, Gotoh H, Yusa S, Tanaka S. 1989. The importance of endotoxin and glucan for symptoms in sick buildings. In: Present and Future of Indoor Air Quality (Bleva CJ, Courtiaux Y, Goaerts M, eds). Amsterdam:Elsevier Science, 219–226.

Schmitt C. 2006. Immune system’s Toll-like receptors have good opportunities for cancer treatment. J Natl Cancer Inst 98(9):574–575.

Schuttefeld D, Beebe-Dimmer J. 2006. Chronic inflammation: a common and important factor in the pathogenesis of cancer. Cancer J 12(3):157–164.

Schroeder JC, Tolbert PE, Eisen EA, Monson RR, Hallock MF, Smith TJ, et al. 1997. Mortality studies of machinist fluid exposure in the automobile industry. IV: a case-control study of lung cancer. Am J Ind Med 31(6):525–533.
