

Appendix 8

Additivity and Synergistic Effects of WTC Hazardous Substances

Introduction

Mixtures of chemicals present some difficulty to the risk and toxicity assessment processes due to the potential effect of one chemical to alter the chemical or toxicological properties of another. Based on numerous experimental studies in many biological systems, the effect or effects of a mixture of chemicals may not be predicted by separately evaluating the effects of each chemical alone. The toxicological interaction of chemicals in a mixture may result in a synergistic or additive effect. Two chemicals are said to act **synergistically** when their combined effect is greater than the sum of the two chemicals acting alone. Two chemicals are said to exert **additive** effects when their combined effects are equal to the sum of the effects of the chemicals acting alone.

The issue of chemical additivity and synergism is particularly important when evaluating exposure to the multiple WTC Hazardous Substances in WTC Dust. Relevant studies reported in the scientific literature regarding the synergistic and additive effects of specific WTC Hazardous Substances were collected and are summarized below. It is noted that the EPA Inspector General's report (EPA, 2003) highlighted the need to consider additive effects of WTC Hazardous Substances in setting appropriate health-based benchmarks and the lack of consideration of these effects in the current COPC benchmarks.

1. Asbestos, PAHs, and PCBs

Polycyclic Aromatic Hydrocarbons (PAHs) were released in the WTC disaster and are also significant toxic components of cigarette smoke. These compounds are not addressed in this report, but the additive toxic effects of asbestos and PAHs in cigarette smoke have been shown through extensive research. Selikoff reported that in a group of asbestos workers, the cigarette smokers were 92 times as likely to develop pulmonary cancers as the nonsmokers (Selikoff et al., 1968). Subsequent studies of this population would seem to indicate that when the lungs have been damaged from asbestos exposure (resulting in asbestosis), the carcinogenic effects of cigarette smoke are enhanced (Jones et al., 1996). One possible mechanism is a smoking-induced decrease in clearance of fibers from the lung by interference with ciliary action or macrophage activity (Plowman, 1982), leading in turn to increased penetration of the

respiratory epithelium by asbestos fibers (Hobson et al. 1988; McFadden et al., 1986). Another possibility is that asbestos fibers (either in air or in the lung) may adsorb carcinogenic substances present in smoke, thereby increasing levels of these substances in the lung (Menard et al., 1986; Mossman et al., 1983b). Research has demonstrated that volatile and/or airborne contaminants such as PAHs can adsorb to chrysotile asbestos fibers forming two-dimensional coatings on the fiber (Fournier and Pezerat, 1986). Furthermore, chrysotile asbestos acts as a better adsorbent for PAHs than do amosite or crocidolite asbestos, glass microfibers, or glass wool (Harvey et al., 1984). Research also indicates that adsorption to asbestos increases the ability of the carcinogenic PAH benzo(a)pyrene to cross biological membranes and enter into cells (Mossman et al., 1983a), enhancing the carcinogenic potential of benzo(a)pyrene (Poole et al., 1983; DiPaolo et al., 1983; Shabad et al., 1974; Kanazawa et al., 1970). During the WTC Event, airborne asbestos released from the collapsing buildings was available for interaction with other airborne toxicants also released from the buildings or with toxic combustion products such as PAHs or PCBs in smoke released from fires. Therefore, simultaneous exposure to asbestos and other toxicants that contaminate the area around the WTC remains a potential hazard and could result in long-term toxicity and co-carcinogenicity due to inhalation of asbestos coated with other compounds.

2. *Particulate Matter (PM) and PAHs*

Similar to asbestos, an important aspect of the health effects of PM is the contribution of hazardous chemicals adsorbed onto the PM that are inhaled or ingested. In addition, the uptake of PAHs into model biological membranes is enhanced when the PAHs are adsorbed onto particulates, most notably silica, carbon black, and chrysotile asbestos fibers (Lakowicz et al., 1978; Lakowicz et al., 1980; Bevan et al., 1981). Based on his results, Lakowicz concluded that particulates could enhance the cellular availability of carcinogens, resulting in a cocarcinogenic effect. Coadministration of benzo[a]pyrene and particulate material greatly increases respiratory tract tumor yields in laboratory animals following intratracheal instillation (Pershagen et al., 1984; Saffiotti et al., 1972; Stenback and Rowland, 1979; Stenback et al., 1976). When benzo[a]pyrene is particle-bound, clearance from hamster lungs is slower than that of pure benzo[a]pyrene aerosol, increasing the length of time the lungs are exposed and increasing the dose to the gastrointestinal tract as a result of mucociliary clearance

(ATSDR, 1995). The potential interactions between combustion products like gaseous emissions and PAHs and vaporized glass, carbon, or asbestos fibers that are then inhaled are not likely under normal circumstances. However, the WTC collapse presented an unusual case where airborne contaminants released from burning fuel sources and other carcinogens mixed with and potentially adsorbed to numerous particulates released as the buildings collapsed. These contaminated particles were not only inhaled by people near the site for weeks after the disaster, but were deposited into surrounding buildings where they pose an ongoing exposure risk.

3. *Lead and Mercury*

Animal studies suggest that lead exacerbates the toxic effects of mercury. In rats, the administration of lead nitrate resulted in increased mercury deposition in the kidney, along with increased lethality (Congiu et al., 1979).

4. *Dioxin and PCBs*

Recent research has demonstrated additive effects of 2,3,7,8-TCDD on tumor promotion and developmental defects when mixed with specific PCBs (Wolfe, 1997; Birnbaum et al., 1985). An additive adverse effect was shown on liver function in rats fed 2,3,7,8-TCDD, different PCBs, or combinations thereof (van Birgelen et al., 1996). PCB 153, when combined with 2,3,7,8-TCDD, also synergistically induced some hepatic enzymes, though this effect was dose- and species-dependent (Bannister and Safe, 1987). These findings demonstrate the importance of dose and the complexity of possible health effects upon exposure to mixtures of toxic compounds. In addition to their additive toxic effects when combined with 2,3,7,8-TCDD or asbestos, PCBs in combination with methylmercury, an organic mercurial compound identified in trace quantities in the Building, were recently shown to greatly alter calcium ion regulation and dopamine secretion in rat brain striatal cells (Bemis and Seegal, 2000; Bemis and Seegal, 1999). These results suggest that a combination of PCBs and methylmercury could have synergistic neurotoxic effects in exposed individuals.