Dragon, Karen E. (CDC/NIOSH/EID)

From: Royce,Bernadette [broyce@ufanyc.org]
Sent: Thursday, April 28, 2011 4:39 PM
To: NIOSH Docket Office (CDC)
Subject: Response to Request for Information on Conditions Relating to Cancer - NOSH Docket #227
Attachments: Syngergism WTC-5.doc

To Whom It May Concern:

Please see the attached document for my submission. Thank you for your time.

Best Regards,

Bernadette Royce

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April 28, 2011

To Whom It May Concern:

I would sincerely appreciate it if the following information would be reviewed with regard to NIOSH Docket #227. Thank you for your time and consideration.

Sincerely:

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- Many of the chemicals found at the World Trade Center site are known carcinogens and also have documented synergistic properties.
- 95% of all toxicological studies have focused on one chemical.
- Of the remaining 5%, the majority of the chemical studies have focused mostly on binary mixtures.
- Regulatory agencies have utilized simplified versions of risk assessment for mixtures, which has been criticized as a technique.
- National Institutes of Health offered grants to study chemical mixtures, recognizing that there was little information on how chemical mixtures affected the body.
- Agency for Toxic Substances and Disease Registry presumes that any chemical that is carcinogenic in animals is carcinogenic in humans.
- ATSDR considers an exposure to carcinogens on a case-by-case basis.
- ATSDR also recognizes importance of additive effects; in absence of contrary information, assume effects are additive.
- ATSDR established the World Trade Center (WTC) Health Registry with the NYC Health Department
- American Conference of Government Industrial Hygienists states that synergistic effects must be determined on an individual basis.
- OSHA 29 CFR 1910.100 has a formula for cumulative exposure to chemicals
- National Contingency Plan 40 CFR 3000.430 utilizes a different risk level "as the point of departure for determining remediation goals for alternatives with Applicable or Relevant and Appropriate Requirements (ARARs) are not available

or are not sufficiently protective because of the presence of multiple contaminants."

- In a 2001 report, the Government Accountability Office (GAO) recognized that one of the criticisms of federal agencies in risk assessment was their failure to account for synergism in multiple chemical exposures.
- Endocrine-disrupting chemicals (EDCs) have been shown to have additive and synergistic effects. Many of the chemicals at WTC site were EDCs.
- Other chemicals at WTC site have synergistic effects for a variety of mechanisms; (asbestos fibers and particulate matter can carry chemicals into lungs).
- Recent study showed chemical interaction between benzene and toluene on lung tissue led to DNA damage.
- In 2003, an EPA report acknowledged that the carcinogens at the WTC site should be considered to have additive effects.

The World Trade Center disaster exposed thousands of rescue workers to a wide variety of toxins, many of which are known carcinogens. Some of the toxins also have known synergistic properties. As the tenth anniversary of 9/11 approaches, a multitude of illnesses have appeared among the rescue workers, including respiratory disease, Gastroesophageal reflux disease, behavioral disorders, and numerous cancers. After nine years, The James Zadroga Bill for 9/11 Health and Compensation Act was approved by Congress and signed by President Obama. However, the Act does not recognize the need to cover cancer as an occupational condition resulting from the massive exposure to the various toxins at the WTC site. NIOSH must consider the biological plausibility that the synergistic effects of these numerous chemicals would lead to increased cancer rates than previously seen in firefighters. This failure to cover cancer as an occupational condition resulting from this significant toxicological exposure at the site needs to be corrected.

The most famous statement in toxicology is "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy" (Paracelsus, 1493-1541). However, the dose studied in this theoretical statement would be a single chemical. Toxicologists have continued to study chemicals as single chemicals in approximately 95% of all chemical studies in order to assess their toxicity (Monosson, 2003, p. 8). The toxicological value of these studies is lacking as it has "become increasingly recognized that humans are not exposed to single chemicals. Rather, humans are exposed either concurrently or sequentially, by various routes of exposure, to a larger number of chemicals from a variety of sources over varying periods of time" (Suk, Olden, & Yang, 2002, p. 891). However, despite these exposures to chemical mixtures, few studies have been conducted on multiple exposures and Material

Safety Data Sheets do not document the potential for additive effects on the human body. Various federal agencies have recognized this failure and documented it in multiple sources. Without studies to determine the effects, most agencies support the concept of additive effects and the biological plausibility of potential toxicity from multiple chemical exposures. This needs to be the basis for understanding the multiple chemical exposures that occurred as a result of the WTC disaster. The WTC situation was an unprecedented public health disaster that scientists have recognized has no known scientific basic with which to compare it to for evaluating the health outcomes. According to Dr. Thomas Cahill of University of California-Davis and the head of the DELTA Group (Detection and Evaluation of Long-range Transport of Aerosols), "No one has ever reported a situation like the one we see in the World Trade Center samples. The air from Ground Zero was laden with extremely high amounts of very small particles, probably associated with high temperatures in the underground debris pile. Normally, in New York City and in most of the world, situations like this just don't exist" (Delta Group, 2002).

The basis of chemical toxicity recognizes several fundamental concepts in its study.

Synergism: when two chemicals, A and B, have a greater combined effect when acting together than either the combined effects of A and B alone. 1 + 1 = 3

Antagonism: when one chemical reduces the toxicity of another chemical

Additive effects: the combined effects of two chemicals are equal to the chemicals acting alone. 1 + 1 = 2

Scientists began to recognize the importance of synergism as early as the 1960s, due to the effects of multiple pharmacological agents within the human body. However, despite this, few studies examine multiple chemicals. "Of the 5% of toxicological studies that do address mixtures, the great majority focus on binary mixtures, or two chemicals at a time, employ relatively high chemical concentrations and observe relatively crude endpoints, or focus on complex mixtures—such as diesel fuel mixtures or contaminated water samples where the chemical composition was unknown" (Monosson, 2003, p. 8).

Both scientists and the law focused on individual chemicals for studies and control of chemical substances (Stewart & Carter, 2009, p. 240). However, many agencies recognized their failure to control and test chemical mixtures. Since the possible permutations of chemical mixtures are limitless, there is virtually no way to test for all the potential synergistic reactions. Toxicological risk assessment has therefore become a difficult task for those assigned to it. "Risk assessment methods cannot possibly account for the complexity of these ever-changing mixtures; hence, regulatory agencies have found it necessary to allow vast simplifications in mixtures risk assessment methods, including simplifications that allow risk assessors to use toxicity data for single chemicals rather than mixtures. The extensive use of simplifications in mixture risk assessment has received sharp criticism and led to legislative mandates that require an increased level of sophistication. For example, provisions in the 1996 U.S. Food Quality Protection Act require the USEPA to assess aggregate exposures from multiple pesticide uses and cumulative toxicity that occur by common mechanisms of toxicity" (Borgert, 2004, p. 620).

The United States government has repeatedly recognized the importance of synergism and additive effects in risk assessment. The various agencies assigned the task of protecting the public and assessing chemical risks have recognized the difficulty of multiple chemical risk assessment and therefore have taken broad attempts to ensure that the potential for synergistic effects are recognized in assessment. Despite this recognition, the government has also admitted that it has failed to assess adequately the risks of synergism in chemical exposures (GAO, 2001, p. 17).

In 1997, the National Institutes of Health offered grants for innovative experiments studying chemical mixtures. In acknowledging that people are exposed not to individual chemicals, but mixtures, NIH stated:

> "not only is there a lack of knowledge concerning the characterization of real-life mixtures based on human exposure or human body burden, but there are limited experimental strategies available that focus on understanding the mechanisms of action of chemical mixtures as it relates to human health. As a consequence, there is limited knowledge of the underlying biological and pathobiological processes associated with how living systems handle chemical mixtures and are affected by them. Moreover, we have limited abilities to predict how chemicals in a mixture interact with each other or biological systems" (NIH, 1997).

NIH (1997) believed that animal studies of chemical mixtures were not particularly useful due to the expense and time required to conduct these studies. For cancer studies, however, the Agency for Toxic Substances and Disease Registry, a federal public health agency, "considers that a substance which has been shown to cause cancer in animals should be presumed to pose a potential carcinogenic risk to humans in the absence of data to the contrary" (ATSDR, 1993). ATSDR (1993) also recognizes that there is no single technique for assessment and "therefore, exposures to carcinogens must be assessed on a case-by-case or context-specific basis."

In their Cancer Policy Framework (1993), ATSDR also recognizes the importance of additive effects. According to the Policy: "Given the paucity of empirical data and the complexity of this issue, ATSDR assumes that, in the absence of information regarding the interaction of these substances, their effects are additive. Such assessments should also be accompanied by a qualitative weight-of-evidence-like statement on the potential for interactive effects, be they potentiating, additive, antagonistic, and/or synergistic" (ATSDR, 1993). ATSDR, along with the NYC Health Department, established the WTC Health Registry in 2002 (New York City website, 2009).

ATSDR is not the only organization that states synergistic effects must be viewed on a case-by-case basis. The American Conference of Government Industrial Hygienists (ACGIH) also states this as their policy considering multiple chemical assessments. In 1989, OSHA changed the permissible exposure limits (PELs) for substances without considering chemical mixtures. "None of these levels, whether guidelines of regulatory requirements are established based on any possible synergistic effects with other chemicals. The only guidance given by the ACGIH for synergistic effects is that such cases must be determined individually" (Lippy & Turner, 1991, p. 81).

In the Code of Federal Regulations, the government recognizes that synergism must be considered in risk assessment. In the Air Contaminants Standard, OSHA has a formula for cumulative exposures of chemicals (29 CFR 1910.1000). In addition, 40 CFR 3000.430 of the National Contingency Plan requires additional considerations for exposure to multiple chemicals.

The Government Accountability Office evaluated the federal agencies that perform risk assessment, including the EPA and OSHA in 2001. While there were

multiple criticisms of how they perform risk assessments, one of these criticisms focused on their lack of assessment of synergism. According to the report: "others, however, criticize agency practices for not being precautionary enough in the face of scientific uncertainties, failing, for example, to adequately account for the synergism of exposures to multiple chemicals or the risks to persons most exposed or most sensitive to a particular toxic agent" (GAO, 2001, p. 17). The report also faulted the agencies for having significant differences in the way they perform risk assessment.

Many of the chemicals present at the WTC site are known to have synergistic effects. Studies have shown that chemicals known as endocrine-disrupting chemicals (EDCs) often act synergistically. "Many EDCs, such as polychlorinated bipheynls, phlthalates, and bisphenol A, interfere with biological signaling mechanisms that govern development, reproduction, or immune function in humans and wildlife....EDCs in combination can produce additive or synergistic effects" (Schwarzman & Wilson, 2009, p. 1065). PCBs and many other chemicals that are or are possible EDCs were "present in measurable quantities, especially in the first 24 to 48 hours after the attacks" at the World Trade Center on 9/11 (Moline et al, 2009, p. 896). The EPA has decided to test benzene this coming year for its potential as an EDC (EPA, 2010). Since a vast number of known or possible EDCs were present in the WTC dust, a synergistic effect is biologically plausible.

Other chemicals in the WTC dust are known to have synergistic effects aside from the EDCs due to a variety of mechanisms. WTC dust included a significant amount of asbestos fibers. "This is of special concern because of the well-described synergistic carcinogenic effects between PAH and asbestos" (Banauch, Dhala, & Prezant,

2005, pp. 162-163). Particulate matter (PM) also has a similar mechanism as the asbestos and allows PAHs to be increasingly adsorbed onto the particles. Other chemicals at the WTC site that are known to have synergistic properties include dioxin and PCBs, as well as mercury and lead (Deutsche Bank Health Group, 2004, p. 37).

A recent study by Pariselli et al (2008) examined the effects of toluene and benzene air mixtures on human epithelial lung cells. Pariselli et al (2008) studied the effects of the singular chemicals and the binary mixture on the cells. Benzene exposure resulted in a depletion of reduced glutathione; this result was not seen with toluene or the toluene/benzene mixture. (Glutathione is a very important antioxidant that prevents cellular damage.) Toluene exposure caused DNA damage; however, the damage was repaired within 24 hours after treatment. Benzene exposure did not result in DNA damage. When the cells were exposed to a mixture of benzene and toluene, there was no change in glutathione status. However, DNA damage did occur and "DNA repair occurring after toluene exposure alone was suppressed in the presence of benzene" (Pariselli et al, 2008, p. 386). Since both these chemicals were present at WTC, the synergistic effects need to be considered as potential cocarcinogens.

The EPA acknowledged in a 2003 report that the carcinogens at the WTC site should be considered to have additive effects. The EPA's goal for asbestos cleanup was a 1 in 10,000 risk for indoor cleanup. However, they did not monitor for other contaminants of potential concern (COPCs), including dioxin and PAHs. "Under Superfund guidance, the risk from exposure to multiple carcinogens is considered additive. Thus, if all three pollutants were cleaned up to levels that equate to a 1-in-10,000 risk for each pollutant, the combined risk would be considered greater than 1-in-

10,000" (EPA, 2003, p. 51). In the months following 9/11, Dr. Cate Jenkins with the EPA wrote in a memo that Lower Manhattan should have been declared a Superfund Site (EHS, 2002).

Multiple chemicals at the WTC site have already been shown to have synergistic potential. Even for those that have not, the agencies that oversee risk assessment for the federal government follow cumulative guidelines regarding multiple chemical situations. They also have policies that state that any chemical with carcinogenic properties in any animal study is believed to be carcinogenic in humans in the absence of evidence to the contrary. The federal agencies have also been faulted by the GAO for not being protective enough concerning the potential for synergism in chemical mixture exposures. The potential for synergism clearly exists at the WTC site and the federal government's position on synergism and additive effects of chemicals has recognized this previously. The possibility for synergistic effects create a strong biological plausibility for carcinogenesis in the rescue workers who spent countless hours being exposed to these various toxins. While epidemiological studies of cancer among these rescue workers may prove of value in the future, unfortunately, the rescue workers diagnosed with cancer do not have time to wait until these studies are completed for the care required to treat the cancer they suffer from now.

Chemical	Carcinogenic	Synergistic
Asbestos	Yes; mesothelioma	With cigarette smoke; large amounts of smoke at scene. Synergistic with PAHs—carcinogenic effects. (Banauch et al, 2005) Individuals exposed to asbestos from Libby Mine, MT also have "significantly higher frequently of positive ANA and ENA tests" Pfau et al (2005) p. 25.
Benzene	Yes-blood cancers	Study has shown synergistic with benzene; leads to DNA damage in human lung cells. (Pariselli et al, 2008)
Toluene	ATSDR: No EPA: cannot be classified	Study has shown synergistic with benzene; leads to DNA damage in human lung cells (Pariselli et al, 2008)
Ethyl benzene	ATSDR: No	Synergistic with noise to produce hearing loss. Cappaert et al (2001).
Propylene	ATSDR: No	
Styrene	ATSDR: No	
Sulfur Dioxide	ATSDR: No	Effect enhanced by aerosols, particularly in submicron range, if both are present at the same time. (WHO, 1979)

Crystalline Silica	IARC: Yes	Tobacco Smoke: numerous MSDS
Lead	ATSDR: No; Known for neurological and hematological effects	Animal studies have indicated a synergistic rxn with lead for behavioral and neurochemical changes in rats (Chandra et al, 1981)
Mercury	ATSDR: Possible Known neurological damage and multiple system damage	Mercury and Carbon Tetrachloride synergistic to result in lipid peroxidation (sign of cell damage) in liver and kidney tissues in male mice (Rungby & Ernst, 1992)
Dioxin	Yes	
PCBs	ATSDR: Reasonably Anticipated	Many EDCs in combination are known to have synergistic effects (Schwarzman & Wilson, 2009)
Chromium	ATSDR: Yes	Synergistic with PAHs to bind at p53 gene in human lung cells (may lead to higher incidence of lung cancer) Feng et al, 2003.
Vermiculite	Normally no; however, this vermiculite was mined from Libby Mine Site, so contained asbestos	Contained Asbestos; Synergistic with PAHs (Banauch et al, 2005)
PAHs	ATSDR: Reasonably Anticipated	Synergistic with asbestos—carcinogenic effects. (Banauch et al, 2005). Synergistic with

		Chromium to bind at p53 gene in human lung cells (may lead to higher incidence of lung cancer) Feng et al, 2003.
Carbon Tetrachloride	ATSDR: Reasonably Anticipated	Synergistic with Bromoform and Chloroform at sub threshold levels; produces liver damage. (Harris et al, 1982).
Nickel	Yes	Synergistic with Cobalt; produces cytotoxic effects; Cross et al (2001)
Bromoform	ATSDR: No	Synergistic with Carbon Tetrachloride at sub threshold levels; produces liver damage. (Harris et al, 1982).
Dioxane	ATSDR: Reasonably Anticipated	
Benzyl-chloride	EPA: Probable human carcinogen IARC: no classification	
Cobalt	ATSDR: Reasonably Anticipated	Synergistic with Nickel; produces cytotoxic effects; Cross et al (2001)
Manganese	ATSDR: No; but known for neurotoxicant properties	Animal studies have indicated a synergistic rxn with lead for behavioral and neurochemical changes in rats (Chandra et al, 1981)
Chloroform	ATSDR:	Synergistic with

	Reasonably Anticipated	Carbon Tetrachloride at sub threshold levels; produces liver damage. (Harris et al, 1982)

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