The Light Brown Apple Moth Aerial Spray Campaign: The Health Hazards of Particles, Toxins, Inflammatory Cascades and Genomic Predisposition

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There are health safety concerns about the use of aerosolized Checkmate LBAM-F spray as a mechanism to address the Light Brown Apple Moth in the San Francisco Bay Area that have not been addressed or investigated.

The ingredients in the proposed Checkmate LBAM-F spray and the spray capsules are a health concern. Neither has been tested in humans. Some of the ingredients, individually, are know to be toxic to humans or animals.

Butylated hydroxytoluene (BHT) and 2-hydroxy-4-n-octylbenzophenone are of particular concern. BHT is used in animal studies to induce lung damage and cancer in areas of the respiratory system that are reachable by the planned spray. BHT is activated into a more potent toxin and then cleared by the major detoxification enzymes cytochrome P450 and glutathione-S-transferase, which are variable in the population.[2] The effects of inhaled BHT in humans have not been studied. The benzophenone in the spray has not been tested but other benzophenones have been found to be stronger endocrine disturbers than bisphenol-A, a very concerning chemical.

The capsule particle size and how it interacts in the human respiratory system is a known health hazard.[3,4] The urea particles in the spray can be expected to reach areas of the lung that can cause damage. Further, the particles and the chemicals they carry can cause damage in the nasal passages and more proximal respiratory tract.

There is a general lack of information about the other ingredients in the spray and any characteristics that may exist when the ingredients are combined[1], making it difficult to make informed decisions about their safety. What we do know is concerning because of the emerging knowledge about how potential chemical toxins interface with individual human biochemistry.

Toxins and noxious particles can set off complex cascades of regulators and inflammation that lead to disease and even cancer. Individual capacity to detoxify toxins varies, making some of the population more vulnerable to harm. When looked at from this 21st century perspective, the spray can conceivably be expected to cause a wide variety of health problems, ranging from increased cardiorespiratory illness to hormone related illness such as breast, reproductive and thyroid illness and even cancers.

Overview

The Checkmate LBAM-F spray is reported to contain the following ingredients: water, (E)-11tetradecen-l-yl acetate (pheromone), (E,E)-9,11 tetradecadien-1-yl acetate (pheromone), ammonium phosphate, 1,2-benzisothiazol-3-one, 2-hydroxy-4-n-octylbenzophenone, cross linked polyurea polymer, butylated hydroxytoluene (BHT), polyvinyl alcohol, tricaprylyl methyl ammonium chloride and sodium phosphate.

The pheromone component is synthetically derived. In this discussion, it will not be differentiated from inert ingredients in keeping with the scientific evidence that both inert and active ingredients can have biologic effects.[1]

Particulate matter is a known health risk. Studies have shown increased mortality from exposure to particulate air pollution from cardiovascular and respiratory disease.[4]

There is the issue of the chemical constituents, alone and in combination, of the proposed spray and their known behavior in biologic systems. There is the lack of study in humans of those constituents, particularly via the proposed aerosolized polymer capsule delivery method. And, there is concern, derived from the accumulating evidence, that individual genetic variation and epigenetics are intricately related to how substances are processed by humans, and vary from person to person.

Thus, while the average of a population may not be adversely affected by an environmental chemical or particulate insult at all, or only at higher doses, individuals with less tolerant genetic predispositions may be more easily affected. Furthermore, since these predispositions are normal variations, they can affect significant percentages of a population. Therefore, this phenomenon should be taken into consideration when making decisions about any substance that will be applied, as the aerial spray program will be. Individuals who are already known to be at increased risk include infants and children, the elderly, and those with respiratory, cardiovascular or cardiopulmonary conditions and people with pre-existing environmental illness.

Lastly, any decision that is made must take into consideration future effects of the spray. We now know that exposure to substances of many types can have effects that become apparent only at a future time, such as hormone disruption, developmental defects, lung disease or cancer. Reliance on short-term symptoms, or lack thereof, as the major determinants of safety is misguided given our current, and growing, knowledge base.

Genetics, Detoxification and Biotransformation

Progress in the understanding of the inter-relationship between environmental exposures and illness manifestations is in its fledgling stages. Nonetheless, much has been discovered and patterns are becoming apparent.

We now know that each person carries within them a collection of genetic polymorphisms, or variations, that code for a wide variety of biochemical enzymes and proteins. Genetic susceptibility appears to be greater at low dose.[2] Furthermore, there is an interconnected web of hormonal and inflammatory feedback mechanisms, with complex systems of receptors, transporters and kinases at play in health and disease. In addition, we have learned that genetics is not as simple as once thought, and that epigenetics may be even more important and immediate in regards to human health. [5]

Humans process substances and toxins for neutralization and removal via a two step detoxification process aptly called phase I and phase II detoxification. These substances can be physiologic products, such as estrogen, or products of external exposure such as environmental toxins. Substances can become more toxic once processed through phase I, with the danger being amplified if phase II is not efficient enough to complete processing of that toxin or if anti-oxidant capacity is insufficient. Increasingly, to understand the mechanism of illness, and of environmental exposure induced illness in particular, it is necessary to understand the intricate system of biotransformation and the variability of genetic predisposition.

This becomes especially important considering that we know through body burden studies that all Americans are accumulating multiple potentially harmful chemicals derived from our environment, within them.[6,7] Environmental chemicals that are lipophilic have the capacity to become stored in body fat indefinitely.

Biochemical enzymes of importance for detoxification include the wide ranging family of cytochrome p450 (CYP 450) enzymes (phase I) and, glutathione-S-transferases (GST), N-acetyl transferases (NAT) and super oxide dismutases (SOD) (phase II) to name a few. For the most part, rather than being "diseased" enzymes, these enzymes differ from individual to individual much the same as the external characteristics of people vary. You could think of it as akin to the consequence seen when a light skinned, blond haired person stays in the sun the same length of time as a darker skinned more sun tolerant person. Same exposure. Different result.

Given the current scientific knowledge base, any discussion of indiscriminate and unavoidable exposure of an entire population to any environmental substance must include knowledge of and acceptance of the biotransformation, carcinogenic, inflammatory, hormonal and other biochemical consequences of such exposure by that substance in order to be fully informed. The science has expanded beyond a simple exposure and symptom production model.

Particle Effects

Of first concern regarding the Checkmate LBAM-F spray is the vehicle of delivery.

An independent analysis by Dennis L. Knepp, Ph.D. and Jeff Haferman, PhD. has shown the polyurea capsule size to be an average of approximately 17 microm and a median of at most 10 microm.[3] Thus, the presence of particles less than or equal to 10 microm can

be expected with the spray. Particle sizes 2.5-10 microm are referred to as PM10 and are considered inhalable into the deeper lung. In comparison, the Consensus Statement of the Department of Pesticide Regulation reports a particle size of 25 microm. Particles of 10 microm can be expected to reach the bronchioles but not the deepest lung.[8] Particles smaller than 10 microm, however, can reach into the lower bronchioles and alveolar areas, with the smallest, theoretically, reaching the deepest.

We know that pollen and subpollen can reach the lower airways.[9] Larger particles can be expected to lodge, be exhaled, be expectorated or be swallowed. Individuals with impaired ciliary sweeping action or cough efforts can be expected to have increased lodging. In a small human study, particles of 6, 8 and 10 microms were inhaled. Retention after 24 hours was 100% in the ciliated bronchioles and 20% in the large and small ciliated airways.[8]

There is no information on how lodging will be affected by the surfactant, tricaprylyl methyl ammonium chloride, or polyvinyl alcohol, the plastic resin emulsifier. The tricaprylyl methyl ammonium chloride MSDS identifies hazard for ingestion and inhalation. Also, mouth breathers would bypass the nasal filtration mechanism. Little is known about the fate of inhaled particles in children, but children may be at increased risk.[10]

We have no data on what will happen to the size of particles as they age. All scenarios involve the dispersal over an extended 30-90 day time period of the chemical contents of the capsules so that at least some constant chemical exposure can be expected. There has been no examination of the deposition pattern and the effect of prolonged repetitive exposure lasting multiple years, to the Checkmate LBAM-F spray in human lung and respiratory tissues. It is unclear how much atmospheric pollutant matter will adhere to the water encased capsules and what additive hazard that will cause.
Particulate mater of the PM10 type has been associated with increased hospital admissions for myocardial infarction, congestive heart failure and possibly ischemic cerebral vascular stroke.[11,12,13] PM10 exposure has also been linked to increased blood coagulation and altered heart rate variability.[14,15]

Multiple studies have found that coarse particles of 2.5-10 microm (PM10) are involved in a pro-inflammatory cascade involving bronchial epithelial cells and alveolar macrophages with cytokines such as TNF (tumor necrosis factor), IL-6 and Cox-2 and increased bone marrow polymorphonuclear leukocytes (PMN) and monocyte production. Toll-like receptors in macrophages appear to be reduced. The inflammatory cascade results in vascular endothelial dysfunction, possibly resulting in PM10 related atherosclerotic vascular events.[16,17,18,19]

Coarse particles of 2.5-10 microm (PM10) are more potent at inducing inflammatory cytokines than smaller particles.[16,20] Coarse PM10 particulate matter has caused inflammation, regardless of the location of sampling and has been associated with increased TNF alpha and glutathione depletion, an indication of oxidative stress, though

oxidative stress appears to be greater at smaller particle size. TNF alpha and IL8 are also seen to extend to sampled blood.[16, 21,22]

It cannot be concluded that larger particles will not have untoward consequences, as particles need not reach the deep lung to have adverse effects. Inflammatory and biotransformation cascades can result from inhalation at the proximal respiratory system as well.[30] Bioorganic pollutants activate toll-like IL-1 receptors, then activating TNFkB, followed by proinflammatory cytokines. Associated metals can induce reactive oxygen species causing damage to lipids, proteins and DNA. Stress activated protein kinases incite activation of transcription factors with chronic inflammatory reactions of the mucous membrane of the upper respiratory tract. Chronic inflammation from constant activation of mucin genes causes goblet cell hyperplasia. This leads to dysregulation and hyperviscous secretion with impaired mucocilliary transport, allowing colonization. The mucous membrane of the nose and tracheobroncheal tree is the most active metabolic organ after the liver.[23,24,25,26,27] It is the site of both phase I and phase II biotransformation with polymorphisms in these enzymes implicated as possible contributors to head and neck tumours.[27,28,29] Xenobiotics have been shown to be metabolized by a wide variety of cytochrome P450 enzymes in multiple areas of the respiratory system, including the bronchial and bronchiolar epithelium, Clara cells, type II pneumocytes and alveolar macrophages.[31]

There has been no study looking at inflammation and biotransformation cascades triggered by the capsules or chemical constituents of the Checkmate spray.

The capsules themselves, cross linked polyurea polymer, could be either urea formaldehyde or phenylhexylurea. We know very little about the actual polymer, its characteristics when inhaled, or, human response to it. We do know that formaldehyde in other inhalation scenarios can produce respiratory, eye, nose and throat irritation. Animal inhalation studies show high acute toxicity. Female workers using urea-formaldehyde resins have shown menstrual disorders. And, the EPA considers formaldehyde to be a probable human carcinogen.[32] There has been no study of the effect of urea on inflammatory and biotransformation cascades.

Aerial spray substances can be expected to redistribute into households via air and foot transport. Studies in communities with pesticide treatment have shown movement of pesticides from outdoors to indoors. Residents in those studies experienced indoor inhalation, dermal contact and oral ingestion of outdoor contaminants. Carpets and fabric were seen to be significant source of accumulation.[33,34,35]

BHT: Mechanisms of Lung and Liver Injury

Butylated Hydroxytoluene (BHT), also known as 2,6-di-tert-butyl-4-methylphenol, is commonly used in studies to induce lung damage and cancer so that they can be studied. The damage from BHT appears to come about because CYP1B1 (cytochrome P450 1B1) biotransforms BHT, during phase I detoxification, into a much more toxic adduct, BHT quinone methide (BHT-QM), which is an unstable electrophile that requires conjugation

to glutathione, a strong antioxidant. Thus, a toxin or carcinogen can be activated by the cytochrome P450 system. Cytochrome P450 enzymes vary from person to person, are determined by genomic predisposition and can be inhibited or induced by various pharmaceutical medications and foods. BHT has also been shown to inhibit GST P1-1 (a glutathione S-transferase enzyme subtype), a phase II enzyme. Thus, when exposed to BHT, it is not only changed into something more toxic (via CYP1B1), but the mechanism to remove that more dangerous toxin during phase II (via GSTP1) is also slowed. The damage is worse when glutathione, a strong anti-oxidant, is depleted. In combination, this serves to compound and prolong toxicity. These effects are seen consistently across many studies.

There are no studies in humans examining inhaled BHT.

BHT is currently banned in food products in, Australia, Japan, Romania and Sweden.

In addition to the more toxic activated forms of BHT, resulting pathologic and compensatory cascades come into play, which in turn can be affected by individual capacity. In mouse lung, BHT metabolized to its more toxic quinone methide (BHT-QM), has been found to substantially increase lipid peroxidation, hydrogen peroxide and superoxide, with inhibition of the anti-oxidant proteins peroxiredoxin 6 (Prx6) and Cu-Zn-superoxide dismutase (SOD1).[36] In mice, BPPOH-QM has been found to be even more toxic than BHTOH-QM and at only half the dose.[37]

Glutathione S-transferase P1-1 is over expressed in tumors. GST P1-1 also protects cells from unstable molecules and oxidants, and plays a regulatory role for stress kinases. GSTP1 has been found to be more abundant than other GST isoforms in tumorigenic cells. Treatment with BHT-QM decreased GSTP1 activity by 28-44%, with inhibition exacerbated by glutathione depletion, thus decreasing cellular protection and influencing cell growth.[38]

Though Checkmate is not a classic pesticide, pesticide-exposed fruit growers with GSTP1 genetic polymorphisms have been found to have increased risk of DNA damage.[39]

Prevalence of GST P1 (+/- and +/+) polymorphisms with reduced efficiency are present in 48 % of the population. GSTP1 is found predominantly in lung, while GSTM1 is found predominantly in liver and is absent in about 50% of the population. GSTT1 activity is deficient in about 20% of Caucasians. Individuals with polymorphisms in all three GST's have been found to be at particularly increased risk for chronic lymphocytic leukemia, perhaps linking the role of environmental toxins to risk for CLL.[40] In addition to its role in detoxification of chemical toxins, CYP1B1 is an important estrogen metabolizing enzyme with variations occurring in normal populations. Medications can also inhibit the efficiency of CYP 1B1. Individuals with polymorphisms can be expected to be at increased risk of complications from exposure to substances utilizing these various detoxification pathways.

The Clara cells of the lung bronchioles appear to be a major source of BHT metabolism and site of BHT induced damage. Clara cells are secretory cells in the bronchioles of the lungs. They protect the bronchiolar epithelium by secreting surfactant and detoxifying harmful inhaled substances. They perform their detoxification duties via cytochrome P450 enzymes. The bronchioles reside between the larger airways and the deep lung and 10 microm particles can be expected to lodge there. Investigation has determined that 10 microm and smaller particles are the smaller end of the spectrum of particle size seen for the Checkmate LBAM-F spray. It is unknown what changes may be seen in particle size, over time, of lodged particles. Furthermore, no testing has been done to see where and how much lodging would be seen in humans of varying age and respiratory characteristics.

In mice, BHTOH, more so than BHT, causes lung damage and tumor development by killing bronchiolar Clara cells and inhibiting lung epithelial gap junction intercellular communication.[41] BHT has also been shown to inhibit epithelial gap junctions in liver as well as lung.[42]

The bronchiolar Clara cells of the lung have been found to be the major site of pulmonary xenobiotic metabolism in mice, converting BHT to the more toxic adduct, BHTOH. Substantial amounts of BHTOH further converted to the even more toxic BHTOH-QM. BHTOH and BHT were both toxic to the Clara cells, and the toxicity and metabolism, as in other studies, was reduced with a CYP450 inhibitor.[43]

BHT has also been seen to cause lung damage with death of alveolar type I pneumocytes and proliferation of subsequent replacement with type II cells via inflammatory response involving bronchiolar Clara cells. [44]

BHT toxicity in not confined to the lung but also affects the liver. BHT has been found to decrease liver cell viability by 80% upon exposure in rats. At the same time, intracellular glutathione levels decreased prior to the onset of cytotoxicity. And, CYP450 inhibition attenuated the toxicity.[45] Electron microscopy of rat liver cells fed BHT has shown widespread hepatotoxicity.[46]

Inflammatory and Immune Manifestations

The use of BHT to induce lung injury in laboratory animals brings up several issues. One is the simple fact that BHT is so commonly used to induce injury. This begs the question of what the effect of extended inhalation and ingestion of BHT in humans would be. The second issue is the variety and cascade of events that it seems capable of setting off and the regulatory mechanisms that are involved. Third, some of the resulting events, such as inflammation, may hold information regardless of how the inflammation was induced and could perhaps be applicable to inflammation of other causation. It appears that inhaled Checkmate capsules will be an additional source of inflammation, as discussed previously.

Severe airway disease with increased mast cells and increased mast cell degranulation has been seen when using BHT to induce lung injury in mice with Forkhead Box F1 (+/- transcriptional factor expressed in endothelial and smooth muscle cells in lung. Increased CXCL12 (chemokine ligand 12, a leukocyte activator and proinflammatory stimulant) was seen, which is essential for mast cell migration and chemotaxis. Looking at embryos, it was found that, during lung development, there was a marked increase in pulmonary mast cells prior to birth, also associated with increased CXCL12 in lung. [47]

Mast cell degranulation in the lung in response to BHT brings up the possible relationship of mast cell degranulation at distant sites as well, such as the intestine. Was the diarrhea reported by some individuals after the 2007 spray mast cell mediated, regardless of the exact spray constituent that may have triggered it? Studies have shown profound ingested allergen induced mast cell mediated diarrhea in the absence of histamine, associated with Th2 intestinal inflammation, IgE, serotonin and platelet-activating factor.[48]

Studies have also found relationships between BHT, inflammation and carcinogenesis. BHT treated mice were found to have common chromosomal locations regulating both inflammation (via cyclooxygenase-2 (COX-2) induction), and carcinogenesis, with the conclusion that pathogenic inflammatory mediators play a role in tumor development.[49] Toll-like receptors (TLR's) have also been found to modulate chronic lung inflammation and tumorigenesis in mice given BHT to induce lung injury.[50]

In addition to its endocrine-disrupting characteristics, benzophenone has also been shown to cause strong polarization to Th2 inflammation via depletion of intracellular glutathione levels and modulation of IL-10 and IL-12 with exacerbation or airway inflammation in an allergic asthma model.[51]

GST polymorphisms have been implicated as increased risk factors for asthma in association with environmental exposures.[52]

The issues of lung irritation, asthma, and emphysema are not a small or theoretical problem. From 2001 to 2003, according to the California Health Interview Survey, asthma and difficulty breathing was found to increase to 6 million individuals. 3.4 million Californians had asthma-like symptoms, such as wheezing, but not classified as asthma. Nineteen percent of children age 5 or under were affected.[53] Also as of 2003, according to the National Conference of State Legislatures, asthma in California cost the state $720 million in direct medical expenses and $544 million in lost school and work days for a cost to the state of greater than $1.2 billion.[54]

Benzophenones and Hormone Disruption

Benzophenones, often used as UV binders, are estrogen receptor binders. The particular benzophenone used in Checkmate LBAM-F, 2-hydroxy-4-n-octyloxybenzophenone, does not appear to have been tested. An extensive testing of potential xenobiotics included benzophenones, but not 2-hydroxy-4-n-octyloxybenzophenone.[55]

In a Japanese study, benzophenone and derivatives were tested for estrogenic activity. Fifteen showed estrogenic activity. Of those benzophenone substances that were estrogenic, four were more estrogenic than bisphenol-A.[56] Bisphenol-A has been associated with developmental abnormalities and the later development of breast cancer on the basis of its estrogenic acivity.

Bisphenol-A, at the time of this writing, is in the process of being banned in Canada for use in baby bottles. A bill has also been introduced into the United States Senate to institute a ban of bisphenol-A in infant and early childhood products. There have been no studies on the effect of long term inhaled benzophenone. But the possibility exists that it is potentially as damaging or more so than bisphenol-A.

Benzophenones have been shown to have estrogenic and anti-androgenic activity. Benzophenone-2 in utero exposure causes hypospadias, perhaps via estrogen receptor signaling.[57] Benzophenones have also been shown to affect not only the estrogen receptors, but also the pituitary, uterus and thyroid. [58]

It appears that benzophenone can affect sex hormone receptors by using a pregnane X receptor (PXR) to activate CYP3A, which in turn induces higher concentrations of effective metabolites leading to endocrine disruption.[59] As with all cytochrome P450 systems, inter-individual variability can be expected. Benzophenone and its metabolites also appear to have genotoxic potential via activation by human P450 2A6 and NADPH-cytochrome P450 reductase, which allowed benzophenones to show umu gene activation.[60]

Thyroid

In addition to effects on the reproductive system, there is increasing evidence that endocrine disturbers affect the thyroid and the hypothalamic-pituitary-thyroid axis.[61]

Benzophenone-2 has been found to inhibit thyroid peroxidase (TPO) more than methimazole or propylthiouricil (PTU), two anti-thyroid medications used for hyperthyroidism, thus having a hypothyroid effect. This was more pronounced in the absence of iodide.[62] Meanwhile, BHT in rat diets has caused increase in iodine uptake.[63]

A Brazilian study found those with GSTP1 polymorphisms to have increased risk for papillary and follicular thyroid carcinomas. [64] If BHT is relevant in the presence of GSTP1 polymorphisms in respiratory tissues, the possibility must be entertained that it could be associated with thyroid illness as well.

Carcinogenesis

The advancements in the understanding of carcinogenesis are rapidly expanding. Key is the incorporation of the concept of genetic predisposition, which is turning out to be multi-factorial rather than single gene related. Some of the single nucleotide

polymorphisms of note include CYP1B1, and the GST family. It is perhaps not surprising then that these polymorphisms present in recurring themes.

As previously described, CYP1B1 is active in the biotransformation of BHT to a toxic BHT-quinone adduct. CYP1B1 is a major enzyme responsible for the formation of 4-hydroxyestradiol, which is genotoxic. CYP1B1 also activates polycyclic aromatic hydrocarbons and heterocyclic aromatic amines, which are mammary carcinogens in animals.

Study has shown that women with breast cancer express variations of glutathione-S-transferase and cytochrome P450 genotypes. Different combinations appear to alter susceptibility to breast cancer and prognosis depending on race, age and environmental exposures. For example, in Caucasian women, CYP1B1 seems to be associated with a poorer prognosis, particularly with the absence of GSTT1.[65,66] Women with CYP1B1 polymorphisms appear to be at higher risk for breast cancer when exposed to xenobiotics that induce CYP1B1. [67]

BHT has also been shown to strongly increase DNA methyl transferase in liver, kidney, heart, spleen, brain and lungs while altering methylation of total DNA and various genes in rats.[68] Localized methylation in the usually unmethylated promoter regions of genes, together with increased expression of DNA methyltransferase, has become a recent important topic of research as an etiology of cancer promotion.[69]

GSTM, GSTP and GSTT appear to be involved in an array of cancers, with environmental toxin exposures that involve them thought to play a part in carcinogen activation.[39,40,64]

Current Directions in Medical Understanding and Pre-Exposure Probability

The stronger the pre event probability, the more likely the association being examined is likely to be true and related. This concept becomes especially important when the characteristics in question are common and could be attributable to a number of things.

The best true and related answers can come only after asking the most pertinent questions. We are just beginning to be able to ask the right questions in the realm of environmental exposures and our evolving view of human biology. Increasingly, these questions not only involve symptom generation, but also, the very earliest precursors to later symptoms.

But truths exist regardless of our ability to ask the right questions or figure out the right answers. An earthquake will happen at whatever magnitude it occurs regardless of our ability to predict it or measure it correctly. Likewise, if a river is dammed and the floodplain developed, when nature's force exceeds the capacity of the riverbank, the river will overflow and the floodplain will flood. The more the insult exceeds the capacity to cope with it, the worse the potential disaster.

As humans, we are not invincible. If we flood our systems with that which exceeds our natural coping capacity, we pay the consequences.

A report by the Office of Environmental Health Hazard Assessment, the Department of Pesticide Regulation and the California Department of Public Health determined there was found to be no causative effect of the September, October and November 2007 Santa Cruz and Monterey spray on reported symptoms.[70] This conclusion was not based upon findings, but rather, upon lack of useful data gathering. However, lack of appropriate data gathering has no bearing on the actual occurrence or non-occurrence of a situation being studied. It simply reflects our inability to document it. It does not reflect the truth. Likewise, data gathered appropriately but absent the right questions does not reflect the truth. Given what is known about the biochemical actions of the chemicals involved in the spray and current knowledge of human biology, there exists the possibility of an increased pre-exposure probability that could make the symptoms reported more likely to be related to the spray than random.

Symptoms reported after the 2007 spray included widespread respiratory system complaints, eye, nose and throat irritation, sinus bleeding and skin rashes. Generalized symptoms included headaches, dizziness, gastrointestinal pain and diarrhea and muscle aches, malaise and fatigue. Breast and menstrual symptoms were reported as were cardiopulmonary symptoms such as tachycardia and arrhythmia. The symptoms reported were common symptoms and potentially attributable to a number of things. But viewed within the time window of the spray, and in conjunction with the known mechanisms of toxicity of some of the spray constituents, together with potential population genomic predisposition and particulate effects, the probability of causative association with the spray is elevated and could potentially make those complaints more probably associated with the spray. This will remain a statistical uncertainty.

An added issue with toxicants in general is the multi-factorial nature of their actions and the systems they affect. This adds layers of complexity that scientific method has difficulty accommodating. However, this relates to our difficulty in devising a method of unbiased study, not on the presence or absence of such multi-factorial actions. It is fair to say that numerous studies are bearing out the previously unrecognized biologic actions of a wide variety of environmental toxins.

Lastly, genomic predisposition testing, including for the polymorphisms discussed in this writing, is in use currently and can be expected to increase, particularly with the likely passage of the Genetic Information Nondiscrimination Act (GINA). Markers of oxidative stress and inflammation are also available. Furthermore, it is likely that our understanding will continue to progress so that relationships that are not apparent or confirmed currently may be so in the not too distant future.

Conclusion

The 21st century has brought with it a new paradigm of biomedical understanding. The advent of biochemical, genetic and epigenetic understanding is incomplete but expanding

rapidly. While we may not know all of the specifics at this point, they will come. What we do know is that new layers of explanation have been opened before us as well as an explosion of questions. Even though it is early, we are discovering a highly integrated and complex web of organization.

What is clear is that individuals experience unique predispositions to illness dictated by individual biochemistry, genetics, epigenetics and exposures. In the majority of cases, illness is a manifestation of placing a normal spectrum of individual biochemistry and genetics into an environment it is ill equipped to cope with, whether it be dietary, habit, stress or environmental exposure. This forces us to come to grips with the likelihood that using averages to make statistical medical decisions, will give way to using meaningful sub areas within the curve, depending upon individual variability. This raises the complexity and challenge of the medical investigations that we use to make complex decisions.

When viewed from this perspective, the symptom complaints after the 2007 Checkmate spray in Monterey and Santa Cruz are more likely to be true, because of heightened pre-event probability, than random. One could even argue that the complaints may have under-represented the true presence of symptoms. We know there is variable genomic predisposition in the detoxification pathways of the population and that at least some of the ingredients of the Checkmate spray are known to interface with these pathways. We know that these pathways can involve complex cascades of inflammation and regulation. We know that there is known hazard associated with particular mater. There exist plausible explanations for lung irritation and toxicity, endocrine disruption, inflammation, immune system triggering and, in some predisposed individuals, depletion of anti-oxidant coping capacity. We know that the particle size of the Checkmate LBAM-F spray can trigger these same complex pathways.

Given what we know, it is reasonable to conclude that, because of individual genomic predisposition and the expected biochemical behavior of the chemicals and encapsulated delivery mechanism involved in the proposed apple moth spray, a percentage of the population can be expected to experience a variety of symptoms and illness from the spray, either immediately or at some time in the future. There exists no testing of the Checkmate LBAM-F product that clarifies any of these specific scientific concerns, nor does there appear to be any plan to do so. Any decision to spray must weigh the danger of the pest, all other available methods to solve the problem, and, whether or not any need to spray justifies the illness that will be caused by the spray, acutely or in the future.

In this author's view, attempting to eradicate the light brown apple moth with this spray is ill advised and not worth inducing the reasonably expected, and significant, illness consequences in the population.

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