Department of Pesticide Regulation

Paul Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

March 26, 2003

Dr. Virginia Moser
B105-04
U.S. EPA Mailroom
109 T W Alexander Drive
Research Triangle Park, NC 27711

Dear Dr. Moser:

Thank you very much for agreeing to examine these two studies with methyl bromide as part of our attempt to obtain the best expert opinions regarding the most appropriate regulatory endpoint for use with exposure for short-term periods. As you can understand from the enclosed documents, there has been a lack of consensus among the scientific reviewers.

This package contains a copy of the earlier study by Newton and the newer study by Schaefer. We have had considerable discussion both internally and with peer reviewers at University of California, Davis, and with stakeholders. The later study is a 6-week inhalation study conducted by WIL and has been the basis for some controversy regarding the interpretation of the results. The package also contains the staff's reviews of both studies and additional letters and memoranda associated with the study by Schaefer. In order to facilitate your review for us, we would like to pose the following questions for your consideration:

Schaefer study

1. What, in your opinion, is the NOEL/LOEL based on the results of the study?

2. What is the quality of the FOB conducted with the dog by WIL from your perspective?

Both studies

1. Considering the two studies, what should be the NOEL for regulatory purposes?

2. Do they complement each other?

3. What would you consider the critical endpoint to use to regulate for short-term exposure to methyl bromide by inhalation?

As suggested to you by Dr. Joyce Gee when she contacted you for me on Tuesday, we will be in contact with you towards the end of next week regarding your progress and when you might be able to complete your review.

Again, we thank you very much for you willingness to give us assistance.

Sincerely,

Gary T. Patterson, Chief
Medical Toxicology Branch
(916) 445-4233

Enclosures

cc: Tobi Jones, Assistant Director
Joyce Gee, Senior Toxicologist

bcc: Paul Gosselin, Chief Deputy Director

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS RESEARCH LABORATORY
NEUROTOXICOLOGY DIVISION
RESEARCH TRIANGLE PARK, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

DATE: April 24, 2003

SUBJECT: Review of methyl bromide study by WIL Research Laboratories

TO: Gary Patterson, Ph.D.
Department of Pesticide Regulation
State of California Environmental Protection Agency

FROM: Ginger Moser, Ph.D.
Neurobehavioral Toxicology Branch/Neurotoxicology Division

At your request, I have reviewed the methyl bromide study conducted at WIL Research Laboratories. I was provided with the study report, letters from outside reviewers (Drs. Janice Chambers, Jerold Last, Kent Pinkerton, and Ms. Judy Buelke-Sam), reviews from within CalEPA, and responses from WIL. The summaries from all these reviewers have been very cogent and valid. However, it is obvious that there are specific areas of disagreement in the interpretation of the data.

Overall, the study design appeared reasonable with adequate opportunities to detect neurobehavioral or toxicological changes, with pre-exposure testing, observations during and after exposures and on non-exposure days, and incorporating clinical observations with FOB evaluations. Most of the evaluations are listed in the EPA FOB guideline, which is intended primarily for rodents, but indeed many of the measures were originally derived from veterinary textbooks which describe neurological examinations (e.g., Oliver and Lorenz, 1983). Motor activity was also measured periodically, and neuropathology conducted at the end of the exposure period.

There are quite a few issues regarding the study, some of which are important for interpretation, and others which are just unfortunate (e.g., accidental exposure of two control dogs, problems with test chamber concentrations). Instead, I focus on the issues below:

1) The one dog that was diagnosed with Idiopathic Febrile Necrotizing Arteritis raises some questions. I have now read several papers on this syndrome as well as spoken with our attending laboratory animal veterinarian, and two other practicing veterinarians, and the overall diagnosis based on the symptoms described is not well-substantiated. However, I would never attempt to contradict the diagnosis of the experts consulted by WIL. Furthermore, the fact that these symptoms did not appear in any other treated dog supports the random nature of the finding, and while there

may be speculation, there simply isn't enough information to lead to a different conclusion. I have to conclude, therefore, that whatever was wrong with this dog was not clearly related to treatment.

2) The toxicologists at WIL should rename the response they are calling "proprioceptive placing". Conducted as described in their operating protocol, this is a visual placing test. This test comes directly from Oliver and Lorenz, in which it is also clearly described as visual placing. Proprioception is quite different, in that it involves awareness of position of the limbs (and returning limbs to normal positions) without actually seeing them. I strongly suggest that the dogs should be held in a somewhat uncomfortable position to produce some incentive to reach out to the table (this is also suggested in Oliver and Lorenz). This small change in the conduct of the test would make the test more robust, and eliminate the need for *post hoc* speculations that the lack of a response was because the dogs had "become accustomed to being held".

The lack of this visual placing response was increased in a dose-dependent but transient manner in the present study. WIL also supplied data from other studies, in which the response was altered in a high-dose dog, and in a control dog. Arguments raised by other reviewers for discounting this finding are:
a) Low incidence: A total of 1/8 (12.5%) dogs in the mid-dose group, and 2/8 (25%) in the high-dose group did not show a normal response at least one time during exposure. This could represent the more sensitive individuals of the group. Testing a higher dose (the high dose was only 4x the low dose) would have provided better opportunity for defining the dose-response.
b) Transient effects: Only one dog (high dose) lacked the response at the end of exposure. While toxicity is often progressive with continued exposure, there are many examples of compensation within the nervous system that results in what appears to be a transient effect. This compensation indicates that the nervous system has indeed been altered, which could be considered a neurotoxic response. In this case, however, the Newton study strongly suggests cumulative effects, so effects at the end of exposure would be expected.
c) Lack of correlative changes: There were no corresponding changes in other sensory tests (especially the visual endpoints) or evidence of sedation or decreased motor function which could account for the lack of response. In the Newton study, sedation was observed at higher concentrations, which could suggest a continuum of effects.

After evaluating these factors, I must conclude that even though this might represent a neurotoxic effect occurring at a threshold dose, a lack of correlative changes and the low incidence do not support using this endpoint <u>alone</u> as the critical effect for the study.

3) The consistent observations of discharge around the eyes and feces-related findings (soft, mucoid feces, and/or diarrhea) are intriguing and could be indicative of stress, illness, or treatment. These findings were listed for control dogs, and these do occur sporadically in normal animals. However, the incidence and persistence of these effects showed a dose-response that is hard to ignore. Indeed, chemical effects may sometimes be expressed as increased incidence in otherwise sporadic changes. While these changes are not neurotoxic *per se*, they may represent a toxic response to chemical exposure.

In the males, two control dogs had "feces findings" a few times, all near the beginning of

exposures. The low dose group also had two dogs with such findings (ignoring #8738), but they occurred later in the course of exposure. All mid-dose dogs had such findings, ranging from once to a few times to essentially every time the dog was examined (one dog). Again, these findings were mostly later in the study. All high-dose dogs also had such findings, with two dogs having it three times each, and the other two showing it at essentially every observation from the beginning of exposure on. The eye discharge followed a similar pattern: none in controls or the two lower dose groups, but two dogs in the high dose that showed this on multiple observations throughout exposure.

Data from the female dogs were more difficult to evaluate, since two controls showed eye discharge on multiple occasions, and one showed feces findings five times. Could this suggest possible ill-health in those dogs to begin with? At the low dose, one dog showed eye discharge throughout exposure, and two others had feces findings a total of six times. At the mid dose, only one dog showed feces findings seven times, and two had eye discharge a few times. At the high dose, feces findings were again reported in three dogs (one to four times each), and eye discharge in three dogs (one to five times each).

I compiled this table from the raw data in the study report. Instead of separating the clinical observations taken at different times, I listed the total number of occurrences for each finding (left and right eyes considered one finding, not two), and the total number of dogs which showed the signs at any time. The only finding that was not treatment-related was the eye discharge in females. My conclusion from this table (not supported by statistics) is that 20 ppm clearly showed evidence of toxicity.

	Occurrences	# Dogs	Occurrences	# Dogs
Sex/Treatment	Feces findings		Eye discharge	
Males				
0	6	2	0	0
5	4	2	0	0
10	21	4	0	0
20	45	4	82	2
Females				
0	8	2	76	2
5	6	2	33	1
10	8	1	3	2
20	15	3	14	3

4) Neuropathological changes were described in almost all the tissues, including control. In fact, every control dog had lesions described as "minimal spinal cord degeneration" and/or "minimal" degeneration of spinal cord roots and peripheral nerves. This occurred in many of the treated dogs as well. It seems that this degeneration should not be such a common finding, and the high incidence of such should be explained.

5) The motor activity data were extremely variable (coefficients of variation from 37% to 87% in control groups), which rendered this measure useless. Activity would have to be decreased by at least 50-90% in a group to be statistically different from controls. Part of this is surely due to the small number of animals tested. The testing laboratory should make efforts to decrease the variability by examining their procedures or equipment.

All of this is a long way of answering your specific questions in your letter dated March 26:

1) My opinion of the NOEL/LOEL, and critical endpoint(s), based on the results of the study:

The high-dose group showed a combination of feces findings (more prominent in males but evident in females), eye discharge (males), and two dogs (one male and one female) not showing the visual placing response. Taken together, this indicates a biological effect at this dose. Therefore, it is my opinion that 20 ppm is a LOEL, and 10 ppm is a NOEL. This dose-response can be reconciled with the Newton study, in which dogs exposed to 50 ppm clearly showed decreased activity and responsiveness during exposures, 100 ppm produced more nervous system depression, and 150 ppm caused frank neurotoxicity.

2) My opinion of the quality of the FOB conducted with the dog by WIL:

It is impossible to judge the expertise of the observers, but the protocol is reasonable and based on well-accepted methods. With the exception of having incorrect terminology for that one endpoint (see # 2 above), the FOB conducted in their laboratory appears to be sound.

I hope that this information is useful for your deliberations of this very important but difficult decision. Please contact me if you need further information, or have questions.

Candidates for Election	
PRESIDENT	**COUNCILOR**
Virginia Moser	Kevin Crofton
David Ray	Gillian Haggerty
	Jacques Maurissen
	Cristina Sunol

Click here to E-Mail your votes: Jordi Llorens

PRESIDENT ELECT CANDIDATE

Virginia ("Ginger") C. Moser

Country of residence: U.S.
Title: Ph.D., D.A.B.T.
Current Position: Supervisory Toxicologist, Chief of the Neurobehavioral, Toxicology Branch, Neurotoxicology Division, U.S. Environmental Protection Agency, Research Triangle Park, N.C., U.S.A.

Biographical sketch and thoughts about INA. My current position is chief of the Neurobehavioral Toxicology Branch, in the Neurotoxicology Division of the U.S. Environmental Protection Agency (EPA). I have been here at the EPA since receiving my Ph.D. in pharmacology and toxicology from the Medical College of Virginia, many years ago. My research focuses on evaluating behavioral, functional, and cognitive changes resulting from various chemical exposures, and determining the neurological or neurochemical mechanisms of such changes. My current research program is directed toward examining developmental neurotoxicity of pesticides and other environmental chemicals, evaluating age-related differences in the response to pesticides, and addressing the assumption of additivity of pesticide mixtures. I have served as an officer in several scientific groups, including Behavioral Toxicology Society (current president-elect), American Board of Toxicology Executive Board of Directors (treasurer), Society of Toxicology Neurotoxicity Specialty Section (councilor), and North Carolina Society of Toxicology (treasurer). I am a member of editorial boards for several journals and have more than 75 published manuscripts and book chapters.

INA is a unique group of international scientists, and the meetings are a rare opportunity to share data and ideas with people that do not usually attend US scientific functions. I would like to use the experience I have gained in other societies to help steer INA into the future. I support an emphasis on student involvement, broadening the focus of meetings, and striving to increase membership and participation.

PRESIDENT ELECT CANDIDATE

David Edward Ray

Country of residence: UK
Title: Ph.D.

United States
Environmental Protection
Agency

Public Affairs (Mail Drop 5)
Research Triangle Park,
North Carolina 27711

For Immediate Release
April 26, 1999

EPA Scientists Receive Agency's Top Honors

Ann Brown, Public Affairs, (919) 541-7818

Research Triangle Park, NC.....A team of scientists at the U.S. Environmental Protection Agency received the Silver Medal Award for superior service, one of the highest awards presented by the Agency to employees, at a ceremony on April l2 in Washington, D.C.

Daewon W. Byun, Ph.D., Joan H. Novak and Jeffrey O. Young, Ph.D., received the prestigious award for their outstanding research achievement in the development of a computer-based modeling system -- the Models-3 Community Multi-Scale Air Quality modeling system -- that can track multiple pollutants simultaneously across states. The model, released last summer, is used by governments, industry and universities to address regional and multiple air pollution issues.

Other employees in the Research Triangle Park who have received EPA Awards are:

- Virginia Moser, Ph.D., received the Science Achievement Award in Human Health for her contributions to the development of a battery of tests that has become the most commonly used screening technique for identifying and characterizing the toxicity of chemicals to the central nervous system.
- David Gemmill, Russell Wiener, Ph.D., Thomas Ward, Larry Cupitt, Ph.D., and John Cline as Team Members received the Contracts Management Award for excellence in supporting the procurement of monitoring instruments to measure fine particles in the air at 1,100 sites in the United States.
- Steven G. Perry, Ph.D., received the James Akerman Award for Ecological Effects Risk Assessment for his contributions to the development of cost-effective methods for evaluating risk to spray drift of pesticides.
- Robin Dennis, Ph.D., as a Team Member received the Science Achievement Award in Water for superior scientific accomplishment in modeling air and water nutrient loads to the Chesapeake Bay for the Chesapeake Bay Program Office 1997 Re-evaluation.

Duke Integrated Toxicology Program

Virginia C. Moser, Ph.D., D.A.B.T.
Toxicologist, Neurotoxicology Division
National Health and Environmental Effects Laboratory
U.S. Environmental Protection Agency

Research Areas: Neurotoxicology
Neurobehavioral Teratology

Education: B.S., Pharmacy, University of North Carolina at Chapel Hill,1977
Ph.D., Pharmacology and Toxicology, Medical College of Virginia, 1983

Research Description:

The focus of this research is to evaluate neurobehavioral consequences of exposure to environmental chemicals in laboratory rats and mice. Initially, efforts in this laboratory were directed toward developing and validating a series of behavioral tests for use in this endeavor; these tests were the basis for the current EPA Test Guidelines for use with pesticides and toxic chemicals. The endpoints include tests of innate behaviors, as well as measures of cognitive function (learning and memory). More recently, we have used these neurobehavioral assessments, along with biochemical measurements, to characterize the neurotoxicity of anticholinesterase pesticides. Current research addresses the issue of age-related differences in response to these pesticides, and using these neurobehavioral evaluations in young, preweanling rats. We have characterized the age-and gender-related differences in response to acute exposure of chlorpyrifos, aldicarb, and methamidophos. We find that age-related differences are compound-specific, and have used that information to develop hypotheses concerning mechanisms to explain these differences. While some sensitivity of the young may be due to underdeveloped detoxification pathways, other qualitative differences exist in comparing the effects in the young and adults, which cannot be explained using kinetic parameters. Research is ongoing to understand better the relationship of the biochemical effects produced by these pesticides and the resultant neurobehavioral alterations. Other research efforts include neurobehavioral evaluation of rats exposed perinatally to pesticides, and analysis of interactions resulting from exposure to pesticide mixtures.

Selected publications:

Moser, VC and S Padilla (1998). Age-and gender-related differences in the time-course of behavioral and biochemical effects produced by oral chlorpyrifos in rats. *Toxicology and Applied Pharmacology* **149**: 107-119.

Moser, VC, PM Phillips, DL Morgan, and RC Sills (1998). Carbon disulfide neurotoxicity in rats: VII. Behavioral evaluations using a functional observational battery. *Neurotoxicology* **19**: 147-158.

Nostrandt, AC, S Padilla, and VC Moser (1997). The relationship of oral chlorpyrifos effects on behavior, cholinesterase inhibition, and muscarinic receptor density in rat. *Pharmacology Biochemistry and Behavior* **58**: 15-23.

Moser, VC, GCBecking, V Cuomo, E Frant'k, BM Kulig, RC MacPhail, HA Tilson, G Winneke, WS Brightwell, MA De Salvia, MW Gill, GC Haggerty, M Hornychov‡, J Lammers, JJ Larsen, KL McDaniel, BK Nelson, and G Ostergaard (1997). The IPCS collaborative study on neurobehavioral screening methods: V. Results of chemical testing. *Neurotoxicology* **18**: 969-1056.

Contact information

 moser.ginger@epamail.epa.gov  (919) 541-5075

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Created Jan 31, 1999 by Frederic Seidler and Everett McCook

Office of Environmental Health Hazard Assessment

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Winston H. Hickox
Agency Secretary

Gray Davis
Governor

MEMORANDUM

4/15 cyp: Jones
Andrews
Patterson
Okumura
Sanders
Segawa
Stanl

TO: Paul Gosselin
Chief Deputy Director
Department of Pesticide Regulation

FROM: Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

DATE: April 9, 2003

SUBJECT: DEVELOPMENT AND CONSULTATION ON METHYL BROMIDE REGULATIONS

Thank you for your March 17, 2003, memorandum regarding the ongoing consultation that our office is providing to your department on the development of methyl bromide regulations based on a sub-chronic reference exposure level (REL). Specifically, you referred to the issue of consistency in health-based recommendations and regulatory approach. This issue was also raised in the April 2, 2003, letter from Paul Helliker to Senator Byron Sher and Assembly Member John Laird.

Specifically, in the current evaluation of methyl bromide by the pesticide program, staff have consulted and included input from the Office of Environmental Health Hazard Assessment's (OEHHA) Air Toxicology Section on the analysis and recommendations concerning the sub-chronic air target level. Note that the Air Toxics Hot Spots Risk Assessment Guidelines, which are undergoing revision pursuant to Senate Bill 25 to specifically account for infants and children, only address the development of acute and chronic RELs and do not have procedures for sub-chronic RELs.

OEHHA's position for both our air toxics and pesticide programs remains as stated in our March 11, 2003, memorandum from Anna Fan to Chuck Andrews that supports a sub-chronic air target level for methyl bromide of no greater than 1 parts per billion (ppb) for children (which does not incorporate additional uncertainty factors). Note that the Department of Pesticide Regulation's (DPR) peer review by the National Academy of Sciences (NAS) was consistent with our recommendations of 1 ppb as a sub-chronic level. The NAS Executive Summary of that peer review states on page 3: "The subcommittee also supports DPR's 6-week RfC's of

2 ppb and 1 ppb for adults and children, respectively, based on a LOAEL of 5 ppm for decreased responsiveness, and spleen weight in dogs."

We appreciate the value you put on our assessments and will continue in providing our consultation to your department on the important issues relating to methyl bromide regulations. If you have any questions, please contact me at (916) 324-2831.

cc: The Honorable Byron Sher
California State Senate
P.O. Box 422848
Sacramento, California 94249-0027

The Honorable John Laird
California State Assembly
P.O. Box 942849
Sacramento, California 94249-0027

Joan E. Denton, Ph. D.
Director
Office of Environmental Health Hazard Assessment

Paul E. Helliker
Director
Department of Pesticide Regulation

From: "Linda McElver" <lmcelver@noacceptablerisk.com>
To: <mmartinez@cdpr.ca.gov>
Date: 3/11/03 4:16PM
Subject: Workshop: Risk Management Considerations for Methyl Bromide Sub chronic Toxicity

March 10, 2003

Workshop: Risk Management Considerations for Methyl Bromide Subchronic Toxicity.

Wednesday, February 26, 2003

What should be the subchronic regulatory goal for Methyl Bromide?

It is unbelievable that our State still practices Junk Science in evaluating chemicals for human safety. Farmers and fumigators do not purchase just Methyl bromide for use. The additive Chloropicrin (tear gas) is used as a warning agent and a pesticide, however all the claims of safety and testing at the sites in our county focus on Methyl Bromide and say nothing about acceptable levels of Chloropicrin.

In the SLO County, Dept. of AG and Public Health Methyl bromide/ chloropicrin Fact sheet of 1998, safety claims are falsely made regarding the full product, but the testing leaves out the synergistic effect of the two: Methyl bromide and Chloropicrin being combined into one product. The toxicity of Chloropicrin is not discussed.

It is very dangerous to only study the toxicity of one pesticide ingredient when another pesticide ingredient is added and never studied as a new entity. Californians have a right to sound science.

A couple of years ago I met at a medical conference Dr. Mohamed B. Abou-Donia, Ph. D. D.A.B.t.,ATS Professor of Pharmacology, Cancer Biology & Neurobiology, Department of Pharmacology and Cancer Biology, Laboratory of Neurotoxicology, Duke University Medical Center, (DUMC 3813, Durham NC 27710, phone 919 684-2221, email donia @acpub.duke.edu). I was quite impressed with him it appears he has made major discoveries using the full products and synergism with other products regarding the gulf war illnesses and the potential mechanism for organophosphate poisoning. This is the caliber of scientist that I would like to see study the effect of the full Methyl Bromide/ Chloropicrin product combined with other medications and common products used by residents to insure the safety of the public. This is the caliber of scientist I would like to see determine a safe level of any pesticide for people with chemical sensitivities like all the people with asthma attacks to the Methyl bromide/chloropicrin. I believe he is aware of a Sensitive Rat model that could be used as a model for chemically intolerant individuals. I have enclosed Multiple Chemical Sensitivity - The End of Controversy an email I received today. I have talked at length with Dr. Martin Pall of Washington State University. He has made the discovery that will end the controversy of Multiple Chemical Sensitivities. While more research is needed, I implore the State of California to stop the residential exposure of Methyl Bromide/Chloropicrin, whether it be in household fumigations or as a neighbor of a farmer until the full impacts of these chemicals can be proven to be safe for people with MCS and other hyper-sensitive populations and vulnerable sub populations. As the paper below indicates we need to inject a safety factor of and additional 1000 to see if it's safe enough for people already getting sick from farm exposures.

Here is the unedited email I received today. I will also forward another version so you can pick up the links.

martin_pall@wsu.edu phone: 509-335-1246
Go to: Fibromyalgia
Go to: Chronic Fatigue Syndrome

Multiple chemical sensitivity (MCS), where people report being exquisitely sensitive to a wide range of organic chemicals, is almost always described as being "controversial." The main source of this supposed controversy is that there has been no plausible physiological mechanism for MCS and consequently, it was difficult to interpret the puzzling reported features of this condition. As discussed below, this is no longer true and consequently the main source of such controversy has been laid to rest. There still are important issues such as how it should be diagnosed and treated and these may also be allayed by further studies of the mechanism discussed below.
The descriptions of MCS made by a several different research groups are remarkably consistent. MCS sufferers report being hypersensitive to a wide variety of hydrophobic organic solvents, including gasoline vapor, perfume, diesel or jet engine exhaust, new or remodeled buildings where building materials or carpeting has outgassed various solvents, vapors associated with copy machines, many solvents used in industrial settings, cleaning materials and cigarette and other smoke. Each of these is known to have volatile hydrophobic organic compounds as a prominent part of its composition. The symptoms of MCS sufferers report having on such solvent exposure include multiorgan pain typically including headache, muscle pain and joint pain, dizziness, cognitive dysfunction including confusion, lack of memory, and lack of concentration. These symptoms are often accompanied by some of a wide range of more variable symptoms. The major symptoms reported on chemical exposure in MCS are strikingly similar to the chronic symptoms in chronic fatigue syndrome (CFS) and may be explained by mechanisms previously proposed for the CFS symptoms (1). Perhaps the best source of information on the properties and science of MCS is the Ashford and Miller book (2). Many individual accounts of MCS victims have been presented in an interesting book edited by Johnson (3). Most MCS sufferers trace their sensitivity to chemicals to a chemical exposure at a particular time in their life, often a single, high level exposure to organic solvents or to certain pesticides, notably organophosphates or carbamates. Some MCS cases are traced to a time period where the person lived or worked in a particular new or newly remodeled building ("sick building syndrome") where the outgassing of the organic solvents may have had a role in inducing MCS. One of the most interesting examples of MCS/sick building syndrome occured about 15 years ago when the U. S. Environmental Protection Agency remodeled its headquarters and some 200 of its employees became chemically sensitive. The obvious interpretation of this pattern of incidence of MCS is that pesticide or high level or repeated organic solvent exposure induces cases of MCS. This interpretation has been challenged by MCS skeptics but they have, in my judgement, no plausible alternative explanation.
MCS in the U. S. appears to be surprisingly common. Epidemiologists have studied how commonly MCS occurs in the U. S. and roughly 9 to 16 % having more modest sensitivity. Thus we are talking about perhaps 10 million severe MCS sufferers and perhaps 25 to 45 million people with more modest sensitivity. From these numbers, it appears that MCS is the most common of what are described as "unexplained illnesses" in the U. S. Those suffering

from severe MCS often have their lives disrupted by their illness. They often have to move to a different location, often undergoing several moves before finding an tolerable environment. They may have to leave their place of employment, so many are unemployed. Going out in public may expose them to perfumes that make them ill. They often report sensitivity to cleaning agents used in motels or other commercial locations. Flying is difficult due to jet fumes, cleaning materials, pesticide use and perfumes.
The exquisite sensitivity of many MCS people is most clearly seen through their reported sensitivity to perfumes. MCS people report becoming ill when a person wearing perfumes walks by or when they are seated several seats away from someone wearing perfume. Clearly the perfume wearer is exposed to a much higher dose than is the MCS person and yet the perfume wearer reports no obvious illness. This strongly suggests that MCS people must be at least 100 times more sensitive than are normal individuals and perhaps a 1000 or more times more sensitive.
Thus a plausible physiological model of MCS must be able to explain each of the following: How can MCS people be 100 to 1000 times more sensitive to hydrophobic organic solvents than normal people? How can such sensitivity be induced by previous exposure to pesticides or organic solvents? Why is MCS chronic, with sensitivity typically lasting for life? How can the diverse symptoms of MCS be explained? Each of these questions is answered by the model discussed below.

Elevated Nitric Oxide/Peroxynitrite/NMDA Model of MCS:

My own interest in MCS stems from the reported overlaps among MCS and chronic fatigue syndrome (CFS), fibromyalgia (FM) and posttraumatic stress disorder (PTSD). These have overlapping symptoms, many people are diagnosed as having more than one of these and cases of each of these are reported to be preceded by and presumably induced by a short term stressor such as infection in CFS and chemical exposure in MCS. The overlaps among these have led others to suggest that they may share a common causal (etiologic) mechanism. Having proposed that elevated levels of nitric oxide and its oxidant product, peroxynitrite are central to the cause of CFS, it was obvious to raise the question of whether these might be involved in MCS. We proposed such a role in a paper published in the Annals of the New York Academy of Sciences (4) and in a subsequent paper, I list 10 different types of experimental observations that provide support for the view that elevated levels of these two compounds have an important role in MCS (5). These 10 observations are listed in the table below (from ref. 5).

Table 1
Types of Evidence Implicating Nitric Oxide/Peroxynitrite in MCS

1. Several organic solvents thought to be able to induce MCS, formaldehyde, benzene, carbon tetrachloride and certain organochlorine pesticides all induce increases in nitric oxide levels.
2. A sequence of action of organophosphate and carbamate insecticides is suggested, whereby they may induce MCS by inactivating acetylcholinesterase and thus produce increased stimulation of muscarinic receptors which are known to produce increases in nitric oxide.
3. Evidence for induction of inflammatory cytokines by organic solvents, which induce the inducible nitric oxide synthase (iNOS). Elevated cytokines are an integral part of a proposed feedback mechanism of the elevated nitric oxide/peroxynitrite theory.
4. Neopterin, a marker of the induction of the iNOS, is reported to be

elevated in MCS.
5. Increased oxidative stress has been reported in MCS and also antioxidant therapy may produce improvements in symptoms, as expected if the levels of the oxidant peroxynitrite are elevated.
6. In a series of studies of a mouse model of MCS, involving partial kindling and kindling, both excessive NMDA activity and excessive nitric oxide synthesis were convincingly shown to be required to produce the characteristic biological response.
7. The symptoms exacerbated on chemical exposure are very similar to the chronic symptoms of CFS (1) and these may be explained by several known properties of nitric oxide, peroxynitrite and inflammatory cytokines, each of which have a role in the proposed mechanism.
8. These conditions (CFS, MCS, FM and PTSD) are often treated through intramuscular injections of vitamin B-12 and B-12 in the form of hydroxocobalamin is a potent nitric oxide scavenger, both in vitro and in vivo.
9. Peroxynitrite is known to induce increased permeabilization of the blood brain barrier and such increased permeabilization is reported in a rat model of MCS.
10. 5 types of evidence implicate excessive NMDA activity in MCS, an activity known to increase nitric oxide and peroxynitrite levels.

However, although one can make a substantial case for this theory for an elevated nitric oxide/peroxynitrite etiology (cause) in MCS, this does not explain how the exquisite chemical sensitivity may be produced - which has to be viewed as the most central puzzle of MCS. By what mechanism or set of mechanisms can such exquisite sensitivity to organic chemicals be generated?

Another theory of MCS was proposed earlier by Iris Bell (6,7) and coworkers and adopted with modifications by numerous other research groups. This was the neural sensitization theory of MCS. What this theory says is that the synapses in the brain, the connections between nerve cells by which one nerve cell stimulates (or in some cases inhibits) another become hypersensitive in MCS. This neural sensitization theory is supported by observations that many of the symptoms of MCS relate directly to brain function and that a number of studies have shown that scans of the brains of MCS people, performed by techniques known as PET scanning or SPECT scanning are abnormal. There is also evidence that electrical activity in the brains of MCS people, measured by EEG's, is also abnormal. Neural sensitization is produced by a mechanism known as long term potentiation, a mechanism that has a role in learning and memory. Long term potentiation produces neural sensitization but in the normal nervous system, it does so very selectively - increasing the sensitivity of certain selected synapses. In MCS, it may be suggested, that a widespread sensitization may be involved that is somehow triggered by chemical or pesticide exposure. This leaves open the question as to why specifically hydrophobic organic solvents or certain pesticides are involved and, most importantly, how these can lead to such exquisite chemical sensitivity as is seen in MCS. So the neural sensitization theory is a promising one but it leaves unanswered the central puzzles of MCS.

The question that I raised in my key paper (5), published in the prestigious publication of the Federation of American Societies for Experimental Biology, The FASEB Journal, is what happens if both of these theories are correct? The answer is that you get a fusion theory that, for the first time, answers all of the most puzzling questions about MCS. The fusion

theory is supported by all of the observations supporting the nitric oxide/peroxynitrite theory, all of the observations supporting the neural sensitization theory plus several additional observations that relate specifically to the fusion.

How can we understand this fusion theory? When you look at the two precursor theories together, you immediately see ways in which they interact with each other. Long term potentiation, the mechanism behind neural sensitization, involves certain receptors at the synapses of nerve cells called NMDA receptors. These are receptors that are stimulated by glutamate and aspartate and when these receptors are stimulated to be active, they produce in turn, increases in nitric oxide and its oxidant product, peroxynitrite. So immediately you can see a possible interaction between the two theories. Furthermore, nitric oxide can act in long term potentiation, serving as what is known as a retrograde messenger, diffusing from the cell containing the NMDA receptors (the post-synaptic cell) to the cell that can stimulate it (the pre-synaptic cell), making the pre-synaptic cell more active in releasing neurotransmitter (glutamate and aspartate). In this way, NMDA stimulation increases the activity to the pre-synaptic cell to stimulate more NMDA activity. Thus we have the potential for a vicious cycle in the brain, with too much NMDA activity leading to too much nitric oxide leading to too much NMDA activity etc (see Figure 1, below). There is also a mechanism by which peroxynitrite may act to exacerbate this potential vicious cycle. Peroxynitrite is known to act to deplete energy (ATP) pools in cells by two different mechanisms and it is known that when cells containing NMDA receptors are energy depleted, the receptors become hypersensitive to stimulation. Consequently nitric oxide may act to increase NMDA stimulation and peroxnitrite may act to increase the sensitivity to such stimulation. With both nitric oxide and peroxynitrite levels increased by NMDA receptor activity, an overall increase in these activities may lead to a major, sustained increase in neural sensitivity and activity. The only thing left is to explain how hydrophobic organic chemicals or pesticides can stimulate this whole response. I'll discuss that below.

I have also proposed two additional, accessory mechanisms in MCS. One is that peroxynitrite is known to act to break down the blood brain barrier - the barrier that minimizes the access of chemicals to the brain. By breaking down this barrier, more chemicals may accumulate in the brain, thus producing more chemical sensitivity. It has been reported that an animal model of MCS shows substantial breakdown of the blood brain barrier. Nitric oxide is also known to inhibit the activity of certain enzymes that degrade hydrophobic organic solvents, known as cytochrome P-450's. By inhibiting these enzymes, nitric oxide will cause more accumulation of these compounds because they are broken down much more slowly. Consequently there are four distinct mechanisms proposed to directly lead to chemical sensitivity:

Nitric oxide acting as a retrograde messenger, increasing release of neurotransmitters (glutamate and aspartate) that stimulate the NMDA receptors.
Peroxynitrite depleted energy (ATP) pools, thus making the NMDA receptors more sensitive to stimulation.
Peroxynitrite acts to break down the blood brain barrier, thus allowing greater chemical access to the brain.
Nitric oxide inhibits cytochrome P-450 activity, thus slowing degradation of hydrophobic organic chemicals.
It is proposed to be the combination of all four of these mechanisms, each

acting at a different level and therefore expected to act synergistically with each other, that produces the exquisite chemical sensitivity reported in MCS.

So how do organophosphate pesticides or hydrophobic organic chemicals initiate this sensitivity and trigger symptoms of MCS? Both are proposed to stimulate the potential vicious cycle involving too much nitric oxide/peroxynitrite and too much NMDA activity (figure 1). Organophosphates and carbamate pesticides, often reported to be involved in inducing cases of MCS, are both acetylcholinesterase inhibitors, acting to increase acetylcholine levels which stimulate muscarinic receptors in the brain. It is known that stimulating of certain muscarinic receptors produces increases in nitric oxide! Thus these two pesticides should be able to act to stimulate the proposed nitric oxide/peroxynitrite/NMDA vicious cycle mechanism. Hydrophobic organic solvents are proposed to act by three possible mechanisms, two producing increases in nitric oxide and one producing energy depletion and therefore NMDA stimulation. These three mechanisms are documented in the scientific literature but none have been tested yet for involvement in MCS. So both the pesticides, organophosphates and carbamates, and the hydrophobic organic solvents have known mechanisms which should be able to initiate the proposed vicious cycle centered on excessive NMDA/nitric oxide/peroxynitrite and thus initiate MCS. Once MCS has been initiated, by simulating this same cycle, they are predicted to produce the symptoms of chemical sensitivity.

Explanations for the most puzzling features reported for MCS:

If this theory is correct, it provides answers to all of the most difficult questions about MCS.

1. How do pesticides (organophosphates and carbamates) and hydrophobic organic solvents act to induce cases of MCS? Each acts to initiate a vicious cycle mechanism involving NMDA receptors, nitric oxide and peroxynitrite in the brain, with organophosphates/carbamates acting via one known mechanism and hydrophobic organic solvents acting by another mechanism.
2. How do hydrophobic organic solvents act to trigger the symptoms of MCS? They act by the same mechanism proposed for such solvents in #1 above.
3. Why is MCS chronic? Presumably for two reasons: Because of the several positive feedback loops that maintain the elevated nitric oxide/peroxynitrite/NMDA activity and also because changes in the synapses of the brain may be long term.
4. How can MCS victims be so exquisitely sensitive to organic solvents? Because there are four different mechanisms by which nitric oxide or peroxynitrite act to produce the response, with the combination of all four acting synergistically to produce such exquisite sensitivity. The mechanisms of all four are well documented although their relevance to MCS can be questioned.
5. How are the symptoms of MCS generated? Possibly by the same mechanisms proposed earlier for the symptoms of chronic fatigue syndrome.
6. How can we explain the overlaps of MCS with chronic fatigue syndrome, fibromyalgia, posttraumatic stress disorder and Gulf War syndrome? All of these are proposed to involve excessive nitric oxide and peroxynitrite and all may also involved excessive NMDA activity.

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Would you trust your doctor if he told you a prescription was safe and they only tested one ingredient, and you got very sick? The pharmaceutical companies advertise on TV all the combinations that they know are dangerous. They say things like this medication is not appropriate for people with liver disease, heart disease, high blood pressure,etc., etc. They don't say they only test one ingredient, but we believe it is safe for everyone.

The public is duped into believing every chemical regulated by the government is as carefully evaluated as medications. Stop lying to the people of this state.

Goal Number 1: Make no safety claims until the full product is tested using both ingredients Methyl Bromide and Cloropicrin.

Questions and Answers about Methyl Bromide/Chloropicrin September 10, 1998

This fact sheet was given to residents in SLO County by the Department of Agriculture and the Department of Public Health, who were getting sick near a strawberry field in San Luis Obispo County. It is unbelievable. It makes false safety claims first by implying that the full product has been tested using Methyl Bromide and Chloropicrin. It was testified at the Sub Chronic

Toxicity hearing that the combination product of Methyl Bromide and Chloropicrin has never been tested and that Chloropicrin was just now being investigated.

It implies that all children are protected. There are no studies on sick animals to approximate what happens to a less than perfect person. It implies that 100 times the limited animal studies will protect every child and every body function. EPA scientists have told me that they believe life threatening asthmatic responses to another pesticide are occurring at the parts per trillion level.

Chloropicrin was added to serve as a warning to people that they were being exposed to Methyl Bromide.

From my Ag office, I was told today that it was discovered that Cloropicrin has pesticidal characteristics. I was also told today that if you experience Cloropicrin symptoms that you are not being exposed to Methyl Bromide because Methyl Bromide separates from the Chloropicrin and Chloropicrin stays lower to the ground. However the fact sheet states that *It is unlikely you have received exposure to methyl bromide unless you experience the symptoms listed above (those of chloropicrin).* This sounds like junk science to me, or that the government is playing Russian Roulette with neighborhoods surrounding the Strawberry Fields.

I have never heard any medical official recommend to continue to expose an asthmatic to a substance shown to be a serious trigger.

The fact sheet also deliberately misleads the public to assuming that all areas of illness have been tested. It clearly states that it takes 21000 parts per billion to show an observable effect in animals. At the hearing the levels were much lower, is the science constantly changing? The Fact sheet says: *Are there minimum human exposure limits for methyl bromide? Yes. The California Department of Pesticide Regulation (DPR) has established a target exposure level to ensure human safety at 210 parts per billion (ppb). This has a built in safety factor. It is 100 times below the highest exposure level that has shown no observable effects to test animals in scientific studies.*

Then it goes on to say that you will feel the effects of Chloropicrin as a warning to exposure to methyl bromide. It also states that Chloropicrin will cause an asthma attack *shortness of breath* burning irritation to the eyes producing tearing, coughing, burning throat* and that Methyl Bromide causes dizziness, headache, nausea, vomiting, weakness. What I want to know is how can the state justify allowing these products continued use when clearly year after year people are getting sick with symptoms of either chloropicrin or Methyl Bromide poisoning. In a report CASE Number A-8 437 Complainant Lynn McDonald, respondent: Morales Ag Services 6 October 1998 8:30 pm. In this case the inspector John Schmitz also experienced symptoms of Chloropicrin poisoning "my eyes began to water", a resident complained that she experienced coughing, burning of the eyes and dizziness last night. While the coughing and burning eyes are chloropicrin the dizziness is from Methyl Bromide. Clearly we need to place the use of this product a mile from any residence. I have just started to go through my counties file on Methyl Bromide cases and it is obvious that a pattern exists and is being ignored by the government. In this particular case the target levels off the site ad extended the buffer zone. But the Methyl Bromide is not stopped. In fact

within 28 ft a .4 parts per million was observed 11 hours later and is well within a toxic exposure level. 5 parts per million has been shown at the hearing to be an exposure to be toxic to a beagle, multiplying it 10 times results in .5 ppm as the so called acceptable level. Obviously with so many complaints this number is not effective. DPR needs to throw out the studies and restrict the use of this product, until it can be determined that full pesticide product won't trigger an asthma attack in a sick child, or a seizure or neurological impairment in a chemically injured person. The study of placing the feet of the beagle on the table as proof of no neurotoxic effect seems bogus. Why not do a brain Spect scan before and after exposure to very sick animals and see if any effect is observed. Why not measure the pulmonary function of mice with asthma or dogs with asthma who have been poisoned by organophosphates like so many Americans have.

DPR needs to look at every sampling and determine from the sampling levels that are affecting the residents. They need to put permanent monitors at all residents reporting health problems. They need to prosecute any farmer that allows drift. They need to ban a product in residential areas if it can not be contained as seen with Methyl Bromide/ Chloropicrin. They need to stop any farmer from ever using this product again if symptoms and exposures to MeBr and Cloropicrin are documented. Since the level of MeBr/ Cloropicrin is still detectable days later, farmers in residential areas should be required to fence their properties to prevent children and others from entering, much the way a home owner is required to fence a yard with a swimming pool, regardless of what chemical is used. I read one report about children playing on the tarps and making holes in them. This is a potential hazardous situation that can not be ignored. A few years back a person in my city crawled under the fumigation tent and died at his residence. I know that when numerous people complained about respiratory distress and other sensitivity reactions to AllerCare a Johnson & Johnson product to kill dust mites, that the EPA did a full investigation and the product was taken off the market.

I am bewildered after reading so many complaints filed and sent to DPR and no investigation has ever been done on the full product or it's suitability in the air when disabled people are present, like people with Multiple chemical Sensitivities, Chronic Fatigue, Fibromyalgia, Asthma and other lung disease, cardio pulmonary depression and other cardiac conditions, seizures and other neurological conditions. My contact within the EPA are suggesting that less than one part per billion is causing life threatening asthma attacks. It is time for DPR to work with Environmental Health agencies instead of just AG agencies, while the Department of Agriculture could monitor exposures in and outside residential homes, environmental health could monitor health before and after fumigation. Suggested tests besides those of Dr.Pall are oximeter monitoring, EEG's, Brain Spect Scans, pulmonary function. I'm sure any of the people who are affected by these so called legal levels would love to prove that this level is not safe. It is so simple and not too expensive to do this, you could make the industry pay since they are so convinced of the safety why would they object. Generally speaking, it is almost impossible to find a doctor that will do any sensitivity testing for toxic chemicals. Sensitive persons are not significant enough to matter to be analyzed or protected. Hospitals in CA don't know how to diagnose pesticide poisoning, there's no test for sensitivity. Buffer zones don't stop the pesticides. Enclosed below is just one of numerous illness complaints. Why is it with these pesticide poisoning complaints does the state fall back on the junk science rather than an

obvious pattern? DPR allows the farmer to continue, even when the air concentrations exceed so called acceptable levels.

In another case A2-209 it was reported that residents) were experiencing lungs shutting down. Why was this not determined to be severe? Shouldn't every asthma attack that has a correlation with a pesticide exposure be treated as an priority one investigation and warrant the continual testing in and outside the home of chloropicrin and Methyl bromide exposures? This site should be banned from any more applications of any pesticide that is synthetic chemical in origin. The EPA should be called in to investigates there are just too many asthma attacks to ignore.

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nrview@thegrid.net

Agricultural Commissioner
2156 Sierra Way
San Luis Obispo, Ca 93401
October 21 2001

RE: Once again neighborhood exposed to methyl bromide

Dear Mr. Richard Greek.

Over the last 16 years you have come to know very well the problems associated with pesticide drift and exposure to the neighbors bordering the strawberry field leased on property owned by The Temple Of The People at the corner of The Pike and South Elm. And please remember, this field was already surrounded by housing before it was changed from a Christmas tree farm to a strawberry field over 20 years ago. The only change is greater housing densities on the south and north sides of this field.

Over these years protection of the neighborhood from drift has been spotty. When the protest levels became intense and covered by the media, only then did your office address the need for better protection. But at least the problems, once accepted, were more or less attempted to be solved within the limits of your abilities and willingness.

One of these problems that was solved in the early 1990* s and reappeared in the mid 1990* s is the size of the nozzle used for applications. The problem reappeared due to the lack of poor record keeping, which you admitted to me, and also due to the lack of institutional memory when the inspector covering this area moved on. If the size of the nozzle is too small, pesticides clouds easily drifted onto adjacent properties.

In the late 1990* s, a solution was found to limit the exposure to leakage of methyl bromide during its application and covered stages with the help of the new inspector, State officials overseeing, ECOSLO and consultation with

me and some neighbors. Instead of fumigating the entire field in one day, the process was spread over a longer time period by fumigating smaller sections of the field in a staggered series. From that change until now everything seemed to be going more or less according to the established protocol. In the prefumigation phase, the field was soaked before plowing to limit chemical dust drift. This had greatly helped us by significantly limiting our exposure to the chemically laced dust. But, your office has yet to study the breakdown components in the dirt nor have you found it necessary to study the process of fog moving chemicals off fields into neighborhoods close or far away or onto other fields and crops.

In late September of 2001, the field was soaked before plowing to limit chemical dust drift as had been done in the previous few years. As a result there were no experiences of dust drift at that time.
Then on September 30, Sunday morning at 8:30 AM, I stepped out the front door to feed our cat, who had been waiting there a while because my wife and I slept in. It was a beautiful sunny and warm morning with no apparent movement of air. I was assaulted by a chemical aroma that had the intensity of a recently enraged skunk. I quickly went back in the house. My wife also experienced the same thing. I called the local office to notify an inspector, but being a Sunday, the recording said to call the San Luis Obispo office number, which I did. I again went out at 9:00. There was now a breeze moving directly west from the ocean into Halcyon and the stench was gone.

On Monday or Tuesday the inspector called; he has yet to visit us as he usually has done in the past when a complaint has been registered. He had been present on the field at the Sunday application but because he, to use his exact words, ³Didn* t see anything wrong,* did not come to our property which has been the focal point of 16 years of expressed concern and known exposure to further ³see* if anything was wrong. His nose would have told him something was definitely wrong. Please note his comment, ³He didn* t see anything wrong.* I asked him, ³How you can see the invisible?* He did not answer that question.

I find this comment of his striking. Over these last few years I have described the unusual air current moments channeled by the area* s local rolling topography and porous tree walls on the east and north sides of the field. I also showed him the inversion layer that sets itself in place over the field on calm days. Its ceiling generally is on level with our kitchen window that is about 4 feet higher than the top of the southern hill overlooking the field. This was adequately illustrated by a fire workers were burning one calm morning at the northern side of the field. The smoke went up in a vertical column and spread southward out over the field. On Friday, October 12, before the breeze picked up, another fire once again illustrated this low layering effect that had a height about equal to our kitchen window, but this time rather than a flat ceiling it displayed a sine wave characteristic slowly moving towards southeast towards us and Halcyon.

By its magnitude, this one exposure on September 30, 2001 exceeds anything we have been directly exposed to at this point in time. I could venture to guess that all the exposures over the last 18 years added together would not meet this particular assault. Our cat was sick by Thursday. She refused to eat or even move. She would not even flick her head after being petted, a usual response not liking her fur to be out of place. By Saturday, October 6, I was experiencing occasional sharp shooting pains in my ears. On Sunday,

the 7th, I woke up with a dry cough and pressure on my lungs. All day long I was only at fifty per cent energy and had a slight fever; it was as if I had a case of the flu, but I knew it was the result of last week* s event. My wife also woke up with pressure on her lungs while out of town visiting a friend. Within two days of her return she was feeling disoriented. We both suffered from headaches during these 2 weeks.

I again called your office on Saturday, October 6, around 7:45 AM to report another event of aroma coming from the last application on the field. The manner in which the field was serviced this year maximized the possibility of leakage around the edges to move into the neighboring properties. The final application was 3U* shaped, going around the eastern, northern and western border. The area that was covered on September 30 was slit open on Sunday, October 7, thereby giving the newly applied area on the eastern side and a portion on the western side additional potential for leakage into the surrounding neighborhood.

I again called your office on the late Friday afternoon of October 12, to report that plowing was taking place without first watering the field. The visible portion of the cloud of dust kicked up by the plow and tractor was at least 20 to 30 feet high and who knows how high the invisible portion reached. The air was calm and so my guess is that the invisible portion of this cloud was spreading out under the inversion ceiling. It is now a week after this last event and so far during this weekend of October 20th and 21st, I have been experiencing an annoying dry cough again. My wife left the area again.

I have had some discussion with neighbors about this series of events and have also heard some second hand accounts. It seems on the west, east and north sides of the field there has been serious exposures with a total of 8 reported cases of illness excluding our cat. On the west side of the field a child had to be taken to a doctor. A neighbor down the street from us had a severe week long asthma attack. Harsh headaches and illness were reported on the northern side of the field over this two week period. Others in the co-housing area, also on the south side of of the field, reported experiencing the assaulting aroma but did not know its source until the field was pointed to.

These first, second and third hand accounts are limited to a very small section of the population around this field. The inspector seems to have made some prejudgments in believing that the gas can not drift until 12 hours after application nor move beyond certain limits without dissipating into 3benign* parts per million features. Though I gave a specific description of intensity, no one from your office came to check for possible sample areas for chemical contamination analysis.

What would your response have been if each of these same eight people claimed to have seen a glassy winged sharper shooter on their property? I would guess that your glassy winged sharp shooter posse would have immediately visited each siting source with the necessary equipment for a thorough examination of the areas and interview each witness. None of this has occurred because it is only people reporting that they have gotten ill from another exposure. And most probably the media would have been called to show what a thorough job your agency did.

The inspector asked if we had seen a doctor. I said no because a blood test

would cost $200.00 or so each of us for a total of at least $400.00. If our blood tests showed contamination, we would be asked where else we might have been exposed (This has happened on more than one occasion, by the way, this asking if it was from elsewhere.). Should the evidence of contamination be accepted, your office maybe would fine the applicator one or two thousand dollars; we would not be reimmersed for our doctor bills. And in the following years once again something would happen because no real significant change would have taken place, just like your lack of serious action over these last 18 years. Action speaks louder than words; we are still being exposed in spite of your limp attempts to solve the problem.

Let me also remind you of some of the past health events on Grell Lane which is on the south side of this field. This history moves from South Elm eastward.

* One house in and on the south side of Grell from South Elm, a couple had to sell their house and move away because the woman kept getting sick whenever there was spraying or plowing.
* This same house was later sold to a third couple. The man in this family gets asthma attacks only during the fumigation cycle.
* One house further in and across the street in the mid 80* s, a woman in her mid 30* s died of cancer.
* In this same house a few years later, a baby was born with a hole in its heart and died.
* In the next house in and on the same side of the street, there was a miscarriage a year later.
* In the house just to our east, a female teenager would always get sick whenever there was spraying of any kind on the field. Her health has been fine now that she no longer lives in this state.
* We experience flu like symptoms and headaches whenever there is spraying. This year was by far the worst. We are getting older, in our late 50* s, and our immune systems, though strong, may be reaching a breaking point. Will be also be forced to sell and move away because your office does not care protect us? This has been going on for the 18 years I have lived here, 16 of which have included signed complaints.

There is also the case of the household on the west side of the field where there is now a serious form of cancer and a child who always has serious asthma attacks during fumigation of the field.

What else is going on in the homes around this field? For years I have asked for your office to do a health survey around this field. You have refused. You have not even educated the neighborhood about what to look for and how to respond to possible exposure. Your failure to do so, I believe, is that you want to keep the area ignorant and limit complaints.

With the advances in technology, there should be some inexpensive black boxes available for placement around fields to detect drift. I have been asking you about this for years as well. At least there should be some low tech monitoring solutions to catch air samples in some kind of container or on some kind of cloth for testing. These could be placed around a field and tested when you receive a complaint.

Please look into this with all seriousness at your command and protect us against any further exposure. I hope that you will address this with all the seriousness that you focus on the current threat to the wine industry. One

would think that people* s health deserve the same scrutiny as the whereabouts of an insect.

Sincerely,

Karl Kempton

cc: County Board of Supervisors
ECOSLO
Environmental Defense Center

Here's a letter from Micheal Kaplan, attachment below.

January 14, 2002

My name is Michael Kaplan. I live at 1728 Tierra Nueva Lane, in the cohousing community adjacent to the strawberry fields in question. Our house is beside the upper parking lot that looks out on the fields; we have a view of them from our second-story bedroom window.

My daughter Leah is 6 years-old. She is a vigorous, robust child who has always demonstrated a hearty constitution. In the past, every illness she experienced lasted briefly and never lingered. During the first week of October, 2001, Leah began to have a loud, persistent dry cough. My wife and I had the same parental instinct: this was a seasonal virus or cold and, with Leah, you wait a day or so until she works through it. This time, she never managed to shake it. Her cough grew worse, severe congestion set in, and then her breathing became labored. In her own words, it felt like there was a ball in her throat. When she tried to take a good, deep breath she started coughing.

When we took Leah to her pediatrician, Dale Rowland, he immediately diagnosed that she was experiencing an asthma attack. During the first of four visits that we made to his office, Dr. Rowland asked us if anything in the environment might have triggered the attack. While we never filed a complaint about the methyl bromide at the time*in fact, we never made any connection to it when Leah first began coughing*we have come to wonder if there is a direct connection between the pesticide application that took place on the 30th, 2nd, 4th and 6th and the sudden deterioration in our little girl*s health.

I come to this hearing understanding the nature of coincidence and circumstantial evidence. On September 30 I walked out of my house around 8 in the morning and experienced a powerful odor all around my residence, which smelled like skunk. Later that day I had a chance to speak with my neighbor Hari Nam Elliot, who said she had smelled the same thing and had lodged a formal complaint. A few days later she told me she had been advised by the Agricultural Department field agent monitoring our local field that the odor had nothing to do with the pesticide application. In fact, it must have been an actual, distressed skunk.

In the three years my family has lived in the cohousing community, we have never had a skunk wander through the premises. Nor have we had one since. No one ever saw a skunk on that particular morning. No one heard the many dogs who live in our backyards barking. Nevertheless, we have been informed that the one time in three years an alleged skunk entered our property just

happened to be the very same day they were applying methyl bromide and chloropricin to the fields below.

That*s a coincidence I can smile at. One of those government-issued ironies that make liberals like myself snicker. But I*m not smiling when I lie awake at night, hearing Leah take short, labored breaths in her sleep. Or when she complains about the ball in her throat that she got during school. Methyl bromide was applied from September 30 to October 6. Leah got sick at the very same time. That*s a dark and difficult coincidence my family is still grappling with.

Has DPR considered that now the EPA is discovering that it's former cancer protection didn't really protect children. I wonder when the government will care about disabled children who are sick, asthmatic or other frail condition and protect them? You can't allow this product to be used in communities with so much evidence of The following is a copy an email I just received.

EPA Seeks to Update Guidelines For Cancer Risk Assessment
Agency Bases Draft Guideline Revisions On Both Public Health Protectiveness and Scientific Soundness;

Draft Supplemental Guidance on Risks from Early-life Exposure Also Issued March 3, 2003

In an effort to update key scientific risk assessment methodologies, EPA has released for public review and comment draft final guidelines for cancer risk assessment, as well as a supplemental guidance for assessing early-life exposure to carcinogens. The release of these draft documents, announced by Dr. Paul Gilman, the Science Advisor to the EPA Administrator and the Assistant Administrator for the Agency*s Office of Research and Development, is an important step in EPA*s revision of cancer risk assessment guidelines first published in 1986. These guidelines provide a framework for EPA scientists to assess possible cancer risks from exposures to environmental pollutants.

EPA has been working to revise the 1986 guidelines in light of significant advances in scientific understanding of how cancer may be caused. EPA*s guiding principle for revisions to the cancer guidelines is that Agency cancer risk assessments be both public health protective and scientifically sound. The draft guidelines have also previously been the subject of public review and independent scientific peer review. Today*s draft document reflects many of the comments and suggestions provided to EPA by various reviewers.

Because the draft final *Guidelines for Carcinogen Risk Assessment* recommend consideration of possible sensitive subpopulations and lifestages (such as childhood), EPA is also releasing for public comment a draft *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens.* The draft supplemental guidance is part of EPA*s response to a 1994 recommendation by the National Research Council that *EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults.* Following public review and comment, this draft supplemental guidance will be peer reviewed by EPA*s Science Advisory Board which is comprised of a distinguished body of non-governmental experts drawn from academia,

industry, and environmental communities.

The draft final cancer guidelines reflect EPA*s evolving approach to cancer risk assessment, resulting from both significant strides in scientific knowledge and in EPA*s experience in applying risk assessment principals and practices. Both the draft final guidelines and the draft supplemental guidance reflect the considerable increase in our fundamental knowledge of the biological processes of cancer, and are expected to enhance EPA*s ability to more accurately assess the carcinogenic potential of environmental contaminants.

Both the draft final guidelines and the draft supplemental guidance are available at: http://epa.gov/ncea/raf/cancer2003.htm.

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DRAFT FINAL GUIDELINES FOR CARCINOGEN RISK ASSESSMENT (EXTERNAL REVIEW DRAFT, FEBRUARY 2003)

Notice:

The related draft document entitled Supplemental Guidance for Assessing Cancer Susceptibility Resulting from Early-Life Exposure to Carcinogens is also available for public comment.

Background: In 1986, EPA published a set of risk assessment guidelines, including Guidelines for Carcinogen Risk Assessment. http://www.epa.gov/ncea/raf/car2sab/guidelines_1986.pdf

These Guidelines set forth principles and procedures to guide EPA scientists in assessing the cancer risks from chemicals or other agents in the environment and to inform the public about these procedures. EPA continues to revise its risk assessment guidelines and to develop new guidelines as experience and scientific understanding evolve. EPA has designed its risk assessment guidelines to be flexible enough to accommodate future scientific advances in science and risk assessment practices. Because this current draft has already benefitted from extensive public comment and multiple rounds of expert scientific review by EPA's Science Advisory Board, the Agency is requesting that public comments focus on discussions of specific science issues that are substantively revised or newly addressed since the publication of the 1999 revised draft cancer guidelines.

Prior Revisions: As part of the revisions process, the Agency published Proposed Guidelines for Carcinogen Risk Assessment in 1996 (61 FR 17960, Apr. 23, 1996). http://cfpub.epa.gov/ncea/raf/cra_prop.cfm

The draft revisions have been subject to extensive public comment and scientific peer review, including three reviews by EPA's Science Advisory Board. In 2001, EPA published a notice (66 FR 59593, Nov. 29, 2001) providing an additional opportunity for public comment on a 1999 draft of the Guidelines. http://cfpub.epa.gov/ncea/raf/cancer.cfm Comments were invited on experience gained in applying previous draft revised Guidelines and on specific issues raised in previous comments by the SAB and the public.

2003 Draft Final Guidelines: As announced in the Federal Register on March 3, 2003, the Draft Final Guidelines for Carcinogen Risk Assessment are being made available for public comment until May 1, 2003. EPA's guiding principle for revisions is that Agency cancer risk assessments be both public health protective and scientifically sound. In particular, the revisions to the Guidelines are intended to make greater use of the increasing scientific understanding of the mechanisms that underlie the carcinogenic process. EPA is especially interested in public comments on the following areas: 1) use of default options; 2) hazard descriptors; 3) mode of action; 4) extrapolation to lower doses; and 5) susceptible populations and lifestages. At the same time, EPA is making available for public comment draft Supplemental Guidance http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55446 describing possible approaches that could be used to assess risks resulting from early life exposure to potential carcinogens.

Citation:

2003. DRAFT FINAL GUIDELINES FOR CARCINOGEN RISK ASSESSMENT (EXTERNAL REVIEW DRAFT, FEBRUARY 2003). OTHER NCEA-F-0644A. 03 Mar 2003. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, 125 pp.

Additional Information:

Comments on this document may be submitted, and viewed, by selecting "search" and then keying in the docket identification number OAR-2003-0008 at EPA Dockets at http://www.epa.gov/edocket/. Alternate means to submit comments are described in the March 3, 2003 Federal Register Notice. All comments must be received by May 1, 2003.

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Downloads:

Draft Final Guidelines for Carcinogen Risk Assessment
http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36765

Federal Register Notice of Availability and Opportunity To Provide Comment
http://www.epa.gov/fedrgstr/EPA-MEETINGS/2003/March/Day-03/m4912.htm

Questions and Answers about the 2003 Draft Final Guidelines for Carcinogen Risk Assessment
http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36769

Fact sheet about the 2003 Draft Final Guidelines for Carcinogen Risk Assessment and the related Draft Supplemental Guidance
http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36770

Summary of the 2003 Draft Final Guidelines for Carcinogen Risk

Assessment
http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36771

Related Entries:

SUPPLEMENTAL GUIDANCE FOR ASSESSING CANCER SUSCEPTIBILITY FROM EARLY-LIFE EXPOSURE TO CARCINOGENS (EXTERNAL REVIEW DRAFT)
Relationship Reason: THIS DOCUMENT AUGMENTS THE DRAFT FINAL GUIDELINES DISCUSSION OF CONSIDERATION OF CHILDHOOD RISKS. THE DOCUMENT DESCRIBES METHODS FOR EPA TO USE IN ASSESSING CANCER RISKS FOLLOWING EXPOSURES THAT OCCUR EARLY IN LIFE.
http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55446

My final comments are concerned for my own health and those with chronic fatigue, and cardiac pulmonary failure when exposed to minute amounts of chemicals. I don't want to die on Route 5 or when exposed in a neighborhood and no investigation is done to determine who murdered me. As I said to Paul Helliker in the video that I am mailing that when the ambulance got to my home after a whiff in the air of a weed and feed product, they couldn't find a pulse. Now I travel with an oximeter and typically since I was poisoned by Dursban it makes perfect sense that I react in a similar manner when driving in agricultural areas. Watching your heart rate decline and then increase when you put on oxygen is a simple test to do for anyone who reports fatigue and asthma. I am outraged that the department of Environmental Health isn't given more authority to diagnose incidents of pesticide poisoning where entire neighborhoods are sickened year after year. Obviously, President Bush's statement that in America everyone counts is false, both the president and our governor could care less if people died from a whiff of a chemical in the air. I am demanding protection for all the disabled sick people currently protected under the California building standards commission new cleaner air disability sign. Sensitive Disabled people should be able to access their homes without being exposed to pesticides. Clearly the use of Methyl Bromide/Chloropicrin is hazardous to Californians, especially those disposable chemically sensitive persons and the full product needs to be tested not separately if people are being exposed to legal levels and exhibiting so many symptoms. Under separate cover I will fax some of the cases regarding Methyl Bromide/Chloropicrin

Sincerely,

Linda J. McElver

President
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From: "Steve Tvedten" <stvedten@earthlink.net>
To: "Paul Helliker" <phelliker@cdpr.ca.gov>
Date: 3/11/03 6:43AM
Subject: Multiple Chemical Sensitivity

Multiple Chemical Sensitivity - The End of Controversy

martin_pall@wsu.edu phone: 509-335-1246
Go to: Fibromyalgia
Go to: Chronic Fatigue Syndrome

Multiple chemical sensitivity (MCS), where people report being exquisitely sensitive to a wide range of organic chemicals, is almost always described as being "controversial." The main source of this supposed controversy is that there has been no plausible physiological mechanism for MCS and consequently, it was difficult to interpret the puzzling reported features of this condition. As discussed below, this is no longer true and consequently the main source of such controversy has been laid to rest. There still are important issues such as how it should be diagnosed and treated and these may also be allayed by further studies of the mechanism discussed below.

The descriptions of MCS made by a several different research groups are remarkably consistent. MCS sufferers report being hypersensitive to a wide variety of hydrophobic organic solvents, including gasoline vapor, perfume, diesel or jet engine exhaust, new or remodeled buildings where building materials or carpeting has outgassed various solvents, vapors associated with copy machines, many solvents used in industrial settings, cleaning materials and cigarette and other smoke. Each of these is known to have volatile hydrophobic organic compounds as a prominent part of its composition. The symptoms of MCS sufferers report having on such solvent exposure include multiorgan pain typically including headache, muscle pain and joint pain, dizziness, cognitive dysfunction including confusion, lack of memory, and lack of concentration. These symptoms are often accompanied by some of a wide range of more variable symptoms. The major symptoms reported on chemical exposure in MCS are strikingly similar to the chronic symptoms in chronic fatigue syndrome (CFS) and may be explained by mechanisms previously proposed for the CFS symptoms (1). Perhaps the best source of information on the properties and science of MCS is the Ashford and Miller book (2). Many individual accounts of MCS victims have been presented in an interesting book edited by Johnson (3). Most MCS sufferers trace their sensitivity to chemicals to a chemical exposure at a particular time in their life, often a single, high level exposure to organic solvents or to certain pesticides, notably organophosphates or carbamates. Some MCS cases are traced to a time period where the person lived or worked in a particular new or newly remodeled building ("sick building syndrome") where the outgassing of the organic solvents may have had a role in inducing MCS. One of the most interesting examples of MCS/sick building syndrome occured about 15 years ago when the U. S. Environmental Protection Agency remodeled its headquarters and some 200 of its employees became chemically sensitive. The obvious interpretation of this pattern of incidence of MCS is that pesticide or high level or repeated organic solvent exposure induces cases of MCS. This interpretation has been challenged by MCS skeptics but they have, in my judgement, no plausible alternative explanation.

MCS in the U. S. appears to be surprisingly common. Epidemiologists have studied how commonly MCS occurs in the U. S. and roughly 9 to 16 % having more modest sensitivity. Thus we are talking about perhaps 10 million severe

MCS sufferers and perhaps 25 to 45 million people with more modest sensitivity. From these numbers, it appears that MCS is the most common of what are described as "unexplained illnesses" in the U. S. Those suffering from severe MCS often have their lives disrupted by their illness. They often have to move to a different location, often undergoing several moves before finding an tolerable environment. They may have to leave their place of employment, so many are unemployed. Going out in public may expose them to perfumes that make them ill. They often report sensitivity to cleaning agents used in motels or other commercial locations. Flying is difficult due to jet fumes, cleaning materials, pesticide use and perfumes.

The exquisite sensitivity of many MCS people is most clearly seen through their reported sensitivity to perfumes. MCS people report becoming ill when a person wearing perfumes walks by or when they are seated several seats away from someone wearing perfume. Clearly the perfume wearer is exposed to a much higher dose than is the MCS person and yet the perfume wearer reports no obvious illness. This strongly suggests that MCS people must be at least 100 times more sensitive than are normal individuals and perhaps a 1000 or more times more sensitive.

Thus a plausible physiological model of MCS must be able to explain each of the following: How can MCS people be 100 to 1000 times more sensitive to hydrophobic organic solvents than normal people? How can such sensitivity be induced by previous exposure to pesticides or organic solvents? Why is MCS chronic, with sensitivity typically lasting for life? How can the diverse symptoms of MCS be explained? Each of these questions is answered by the model discussed below.

Elevated Nitric Oxide/Peroxynitrite/NMDA Model of MCS:

My own interest in MCS stems from the reported overlaps among MCS and chronic fatigue syndrome (CFS), fibromyalgia (FM) and posttraumatic stress disorder (PTSD). These have overlapping symptoms, many people are diagnosed as having more than one of these and cases of each of these are reported to be preceded by and presumably induced by a short term stressor such as infection in CFS and chemical exposure in MCS. The overlaps among these have led others to suggest that they may share a common causal (etiologic) mechanism. Having proposed that elevated levels of nitric oxide and its oxidant product, peroxynitrite are central to the cause of CFS, it was obvious to raise the question of whether these might be involved in MCS. We proposed such a role in a paper published in the Annals of the New York Academy of Sciences (4) and in a subsequent paper, I list 10 different types of experimental observations that provide support for the view that elevated levels of these two compounds have an important role in MCS (5). These 10 observations are listed in the table below (from ref. 5).

Table 1
Types of Evidence Implicating Nitric Oxide/Peroxynitrite in MCS

1. Several organic solvents thought to be able to induce MCS, formaldehyde, benzene, carbon tetrachloride and certain organochlorine pesticides all induce increases in nitric oxide levels.
2. A sequence of action of organophosphate and carbamate insecticides is suggested, whereby they may induce MCS by inactivating acetylcholinesterase and thus produce increased stimulation of muscarinic receptors which are known to produce increases in nitric oxide.
3. Evidence for induction of inflammatory cytokines by organic solvents, which induce the inducible nitric oxide synthase (iNOS). Elevated

cytokines are an integral part of a proposed feedback mechanism of the elevated nitric oxide/peroxynitrite theory.

4. Neopterin, a marker of the induction of the iNOS, is reported to be elevated in MCS.

5. Increased oxidative stress has been reported in MCS and also antioxidant therapy may produce improvements in symptoms, as expected if the levels of the oxidant peroxynitrite are elevated.

6. In a series of studies of a mouse model of MCS, involving partial kindling and kindling, both excessive NMDA activity and excessive nitric oxide synthesis were convincingly shown to be required to produce the characteristic biological response.

7. The symptoms exacerbated on chemical exposure are very similar to the chronic symptoms of CFS (1) and these may be explained by several known properties of nitric oxide, peroxynitrite and inflammatory cytokines, each of which have a role in the proposed mechanism.

8. These conditions (CFS, MCS, FM and PTSD) are often treated through intramuscular injections of vitamin B-12 and B-12 in the form of hydroxocobalamin is a potent nitric oxide scavenger, both in vitro and in vivo.

9. Peroxynitrite is known to induce increased permeabilization of the blood brain barrier and such increased permeabilization is reported in a rat model of MCS.

10. 5 types of evidence implicate excessive NMDA activity in MCS, an activity known to increase nitric oxide and peroxynitrite levels.

However, although one can make a substantial case for this theory for an elevated nitric oxide/peroxynitrite etiology (cause) in MCS, this does not explain how the exquisite chemical sensitivity may be produced - which has to be viewed as the most central puzzle of MCS. By what mechanism or set of mechanisms can such exquisite sensitivity to organic chemicals be generated?

Another theory of MCS was proposed earlier by Iris Bell (6,7) and coworkers and adopted with modifications by numerous other research groups. This was the neural sensitization theory of MCS. What this theory says is that the synapses in the brain, the connections between nerve cells by which one nerve cell stimulates (or in some cases inhibits) another become hypersensitive in MCS. This neural sensitization theory is supported by observations that many of the symptoms of MCS relate directly to brain function and that a number of studies have shown that scans of the brains of MCS people, performed by techniques known as PET scanning or SPECT scanning are abnormal. There is also evidence that electrical activity in the brains of MCS people, measured by EEG's, is also abnormal. Neural sensitization is produced by a mechanism known as long term potentiation, a mechanism that has a role in learning and memory. Long term potentiation produces neural sensitization but in the normal nervous system, it does so very selectively - increasing the sensitivity of certain selected synapses. In MCS, it may be suggested, that a widespread sensitization may be involved that is somehow triggered by chemical or pesticide exposure. This leaves open the question as to why specifically hydrophobic organic solvents or certain pesticides are involved and, most importantly, how these can lead to such exquisite chemical sensitivity as is seen in MCS. So the neural sensitization theory is a promising one but it leaves unanswered the central puzzles of MCS.

The question that I raised in my key paper (5), published in the prestigious publication of the Federation of American Societies for

Experimental Biology, The FASEB Journal, is what happens if both of these theories are correct? The answer is that you get a fusion theory that, for the first time, answers all of the most puzzling questions about MCS. The fusion theory is supported by all of the observations supporting the nitric oxide/peroxynitrite theory, all of the observations supporting the neural sensitization theory plus several additional observations that relate specifically to the fusion.

How can we understand this fusion theory? When you look at the two precursor theories together, you immediately see ways in which they interact with each other. Long term potentiation, the mechanism behind neural sensitization, involves certain receptors at the synapses of nerve cells called NMDA receptors. These are receptors that are stimulated by glutamate and aspartate and when these receptors are stimulated to be active, they produce in turn, increases in nitric oxide and its oxidant product, peroxynitrite. So immediately you can see a possible interaction between the two theories. Furthermore, nitric oxide can act in long term potentiation, serving as what is known as a retrograde messenger, diffusing from the cell containing the NMDA receptors (the post-synaptic cell) to the cell that can stimulate it (the pre-synaptic cell), making the pre-synaptic cell more active in releasing neurotransmitter (glutamate and aspartate). In this way, NMDA stimulation increases the activity to the pre-synaptic cell to stimulate more NMDA activity. Thus we have the potential for a vicious cycle in the brain, with too much NMDA activity leading to too much nitric oxide leading to too much NMDA activity etc (see Figure 1, below). There is also a mechanism by which peroxynitrite may act to exacerbate this potential vicious cycle. Peroxynitrite is known to act to deplete energy (ATP) pools in cells by two different mechanisms and it is known that when cells containing NMDA receptors are energy depleted, the receptors become hypersensitive to stimulation. Consequently nitric oxide may act to increase NMDA stimulation and peroxnitrite may act to increase the sensitivity to such stimulation. With both nitric oxide and peroxynitrite levels increased by NMDA receptor activity, an overall increase in these activities may lead to a major, sustained increase in neural sensitivity and activity. The only thing left is to explain how hydrophobic organic chemicals or pesticides can stimulate this whole response. I'll discuss that below.

I have also proposed two additional, accessory mechanisms in MCS. One is that peroxynitrite is known to act to break down the blood brain barrier - the barrier that minimizes the access of chemicals to the brain. By breaking down this barrier, more chemicals may accumulate in the brain, thus producing more chemical sensitivity. It has been reported that an animal model of MCS shows substantial breakdown of the blood brain barrier. Nitric oxide is also known to inhibit the activity of certain enzymes that degrade hydrophobic organic solvents, known as cytochrome P-450's. By inhibiting these enzymes, nitric oxide will cause more accumulation of these compounds because they are broken down much more slowly. Consequently there are four distinct mechanisms proposed to directly lead to chemical sensitivity:

a.. Nitric oxide acting as a retrograde messenger, increasing release of neurotransmitters (glutamate and aspartate) that stimulate the NMDA receptors.

b.. Peroxynitrite depleted energy (ATP) pools, thus making the NMDA receptors more sensitive to stimulation.

c.. Peroxynitrite acts to break down the blood brain barrier, thus allowing greater chemical access to the brain.

d.. Nitric oxide inhibits cytochrome P-450 activity, thus slowing degradation of hydrophobic organic chemicals.

It is proposed to be the combination of all four of these mechanisms, each acting at a different level and therefore expected to act synergistically with each other, that produces the exquisite chemical sensitivity reported in MCS.

So how do organophosphate pesticides or hydrophobic organic chemicals initiate this sensitivity and trigger symptoms of MCS? Both are proposed to stimulate the potential vicious cycle involving too much nitric oxide/peroxynitrite and too much NMDA activity (figure 1). Organophosphates and carbamate pesticides, often reported to be involved in inducing cases of MCS, are both acetylcholinesterase inhibitors, acting to increase acetylcholine levels which stimulate muscarinic receptors in the brain. It is known that stimulating of certain muscarinic receptors produces increases in nitric oxide! Thus these two pesticides should be able to act to stimulate the proposed nitric oxide/peroxynitrite/NMDA vicious cycle mechanism. Hydrophobic organic solvents are proposed to act by three possible mechanisms, two producing increases in nitric oxide and one producing energy depletion and therefore NMDA stimulation. These three mechanisms are documented in the scientific literature but none have been tested yet for involvement in MCS. So both the pesticides, organophosphates and carbamates, and the hydrophobic organic solvents have known mechanisms which should be able to initiate the proposed vicious cycle centered on excessive NMDA/nitric oxide/peroxynitrite and thus initiate MCS. Once MCS has been initiated, by simulating this same cycle, they are predicted to produce the symptoms of chemical sensitivity.

Explanations for the most puzzling features reported for MCS:

If this theory is correct, it provides answers to all of the most difficult questions about MCS.

1. How do pesticides (organophosphates and carbamates) and hydrophobic organic solvents act to induce cases of MCS? Each acts to initiate a vicious cycle mechanism involving NMDA receptors, nitric oxide and peroxynitrite in the brain, with organophosphates/carbamates acting via one known mechanism and hydrophobic organic solvents acting by another mechanism.
2. How do hydrophobic organic solvents act to trigger the symptoms of MCS? They act by the same mechanism proposed for such solvents in #1 above.
3. Why is MCS chronic? Presumably for two reasons: Because of the several positive feedback loops that maintain the elevated nitric oxide/peroxynitrite/NMDA activity and also because changes in the synapses of the brain may be long term.
4. How can MCS victims be so exquisitely sensitive to organic solvents? Because there are four different mechanisms by which nitric oxide or peroxynitrite act to produce the response, with the combination of all four acting synergistically to produce such exquisite sensitivity. The mechanisms of all four are well documented although their relevance to MCS can be questioned.
5. How are the symptoms of MCS generated? Possibly by the same mechanisms proposed earlier for the symptoms of chronic fatigue syndrome.
6. How can we explain the overlaps of MCS with chronic fatigue syndrome, fibromyalgia, posttraumatic stress disorder and Gulf War syndrome?

All of these are proposed to involve excessive nitric oxide and peroxynitrite and all may also involved excessive NMDA activity.

References:

1. .Pall M. L. (2000) Elevated peroxynitrite as the cause of chronic fatigue syndrome: other inducers and mechanisms of symptom generation. J Chronic Fatigue Syndr 7(4),45-58.
2. Ashford N.A., Miller C. (1998) Chemical Exposures: Low Levels and High Stakes, John Wiley and Sons, Inc., New York.
3. Johnson A., ed. (2000) Casualties of Progress. MCS Information Exchange, Brunswick ME.
4. Pall M. L., Satterlee J. D. (2001) Elevated nitric oxide/peroxynitrite mechanism for the common etiology of multiple chemical sensitivity, chronic fatigue syndrome and posttraumatic stress disorder. Ann NY Acad Sci 933,323-329.
5. Pall M. L. (2002) NMDA sensitization and stimulation by peroxynitrite, nitric oxide and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. FASEB J 16,1407-1417.
6. .Bell I. R., Miller C. S., Schwartz G. E. (1992) An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. Biol Psychiatry 32,218-242.
7. Bell I. R., Baldwin C. M., Fernandez M., Schwartz G. E. (1999) Neural sensitization model for multiple chemical sensitivity: overview of theory and empirical evidence. Toxicol Ind Health 15,295-304.

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Email to Linda McEdwen sent from her to DK as attachment

From: <MKap926@aol.com>
To: <linda@noacceptablerisk.com>
Date: 3/10/03 9:17PM
Subject: my daughter's asthma

Linda, here's the tostimony I gave at the Health Commission hearing in January of 2002. Please write back if you have any questions.

Best,
Michael Kaplan

January 14, 2002

My name is Michael Kaplan. I live at 1728 Tierra Nueva Lane, in the cohousing community adjacent to the strawberry fields in question. Our house is beside the upper parking lot that looks out on the fields; we have a view of them from our second-story bedroom window.

My daughter Leah is 6 years-old. She is a vigorous, robust child who has always demonstrated a hearty constitution. In the past, every illness she experienced lasted briefly and never lingered. During the first week of October, 2001, Leah began to have a loud, persistent dry cough. My wife and I had the same parental instinct: this was a seasonal virus or cold and, with Leah, you wait a day or so until she works through it. This time, she never managed to shake it. Her cough grew worse, severe congestion set in, and then her breathing became labored. In her own words, it felt like there was a ball in her throat. When she tried to take a good, deep breath she started coughing.

When we took Leah to her pediatrician, Dale Rowland, he immediately diagnosed that she was experiencing an asthma attack. During the first of four visits that we made to his office, Dr. Rowland asked us if anything in the environment might have triggered the attack. While we never filed a complaint about the methyl bromide at the time--in fact, we never made any connection to it when Leah first began coughing--we have come to wonder if there is a direct connection between the pesticide application that took place on the 30th, 2nd, 4th and 6th and the sudden deterioration in our little girl's health.

I come to this hearing understanding the nature of coincidence and circumstantial evidence. On September 30 I walked out of my house around 8 in the morning and experienced a powerful odor all around my residence, which smelled like skunk. Later that day I had a chance to speak with my neighbor Hari Nam Elliot, who said she had smelled the same thing and had lodged a formal complaint. A few days later she told me she had been advised by the Agricultural Department field agent monitoring our local field that the odor had nothing to do with the pesticide application. In fact, it must have been an actual, distressed skunk.

In the three years my family has lived in the cohousing community, we have never had a skunk wander through the premises. Nor have we had one since. No one ever saw a skunk on that particular morning. No one heard the many dogs who live in our backyards barking. Nevertheless, we have been informed that the one time in three years an alleged skunk entered our property just happened to be the very same day they were applying methyl bromide and chloropricin to the fields below.

That's a coincidence I can smile at. One of those government-issued ironies that make liberals like myself snicker. But I'm not smiling when I lie awake at night, hearing Leah take short, labored breaths in her sleep. Or when she complains about the ball in her throat that she got during school. Methyl bromide was applied from September 30 to October 6. Leah got sick at the very same time. That's a dark and difficult coincidence

my family is still grappling with.