

EXPOSURE AND INTERACTION

The Potential Health Impacts of Using Multiple Pesticides

A CASE STUDY OF THREE COMMONLY USED FUMIGANTS

Conventional agriculture relies heavily on pesticides, often applied as mixtures. Because most pesticides are dangerous to humans, plants, and animals, California's Department of Pesticide Regulation (DPR) controls their use. Pesticides are regulated individually, yet there is evidence that people are regularly exposed to multiple pesticides simultaneously or sequentially.

This case study of three fumigant pesticides commonly applied together in California demonstrates:

1. These pesticides may interact to increase the health risk for California farm workers and residents,
2. Workers and residents are regularly exposed to two or more of these pesticides simultaneously, and
3. DPR does not regulate the application of multiple pesticides to prevent or decrease risks to human health, despite having authority to do so.

THESE PESTICIDES MAY INTERACT TO INCREASE HUMAN HEALTH HAZARD

Each of the pesticides (chloropicrin, Telone®, and metam salts) causes adverse health effects in humans or animals, including acute, developmental, reproductive, and neuro-toxicity, and carcinogenicity and mutagenicity.

There is a reasonable likelihood that the three pesticides can interact to synergistically increase the toxicity to humans. There are three critical ways these pesticides may interact:

1. Decrease the Body's Ability to Detoxify

The human body has a number of mechanisms to remove or neutralize toxic substances. However, those detoxification processes have limits; they can be overwhelmed by excessive exposure to toxins like pesticides. All three pesticides are likely to consume some of the resources the body uses to detoxify. This may lead to an increase in the time it takes for the body to eliminate other compounds. The result is likely to be that toxic compounds have a longer opportunity to damage cells.

2. Attack and Damage DNA

All three fumigants are genotoxic, meaning they damage genetic information within a cell, causing mutations, DNA strand breaks, or chromosomal aberrations. Studies indicate chemical mixtures can have synergistic effects on genotoxicity.^{i,ii} Further testing is needed to determine whether the genotoxicity of these compounds is additive or synergistic.

The Pesticides:

Millions of pounds used in California in 2013:

Chloropicrin

Sensory and respiratory irritant. Evidence of developmental toxicity and carcinogenicity. Used as a warfare agent in World War I.

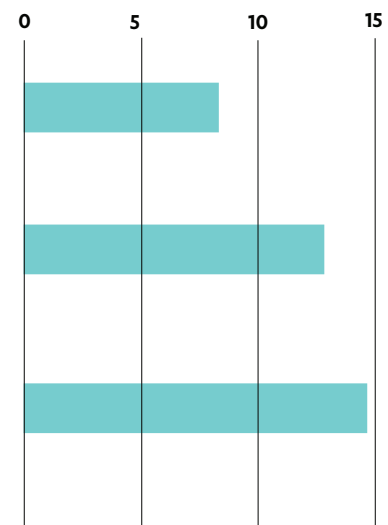
Telone® (1,3-dichloropropene)

Probable carcinogen. Correlation between incidence of pancreatic cancer and long term residence near Telone use. Acute toxicity when inhaled.

Metam Salts

Degrades into MITC. 1991 spill in Dunsmir, CA decimated 40-miles of river. Degrades to Bhopal compound. Developmental, reproductive and neurological toxin.





All three are fumigants, which means they are often airborne. They are used regularly in California on high value crops like strawberries, tomatoes, stone fruits, and tree nuts.



Glutathione is an important molecule that is consumed by the metabolism of toxic substances. The body constantly replenishes glutathione. All three pesticides are known to consume glutathione when they are metabolized, leading to a possible shortage of this key detoxification cofactor.ⁱⁱⁱ

Known Health Effects of the Three Fumigants

(As determined by state or national authority)

	Chloropicrin	Telone	Metam Sodium
 Immediate poisoning of lungs, skin, or digestive track	X	X	X
 Can cause cancer	X	X	X
 Can impact pregnancy, fertility, or child development	X	*	X
 Can damage brain or nervous system	?	X	X

* No evidence of developmental or reproductive toxicity, but only two studies have been conducted. Subsequent experiments may suggest additional toxicity.

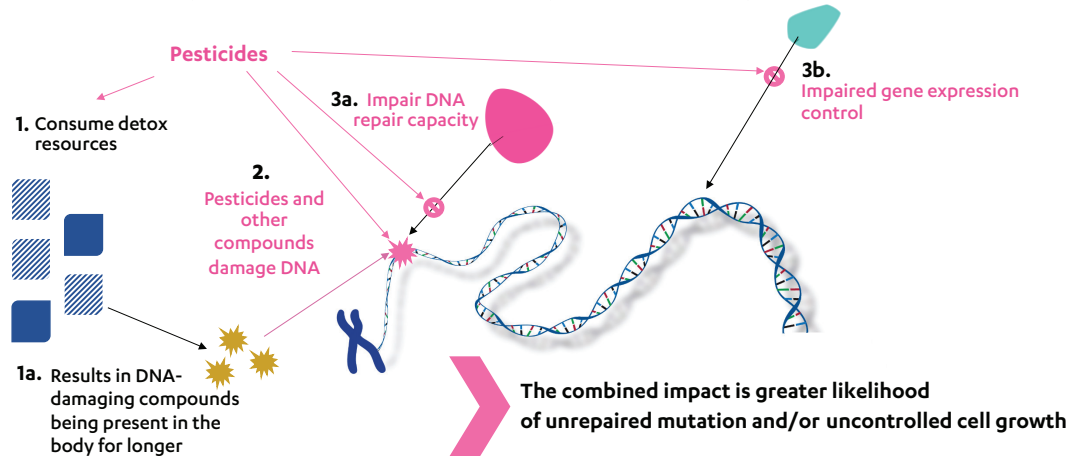
3. Disable DNA Repair and Expression Enzymes

Enzymes that play important roles in gene expression and DNA repair are likely to be damaged by these pesticides. All three pesticides are electrophiles—i.e. they seek out negatively charged electrons. Electrophilic chemicals can attack sulfhydryl and amine groups in proteins. If these groups are located in the enzymes' "active site," the pesticides can disable the enzyme. There are DNA repair enzymes with sulfhydryl and amine groups in their active sites, and it is likely that the pesticides will disable some of these enzymes. There is also a sulfhydryl group in the active site of an enzyme that controls gene expression, which may be impacted by these pesticides. This means these pesticides may work together to prevent the body's enzymes from repairing damaged DNA and may alter gene expression.

Taken together, these three possible interactive effects would result in a greater likelihood of unrepaired mutations and/or uncontrolled cell growth. This would potentially increase the likelihood of cancer. This presents a serious health concern because, as the next section will show, Californians are regularly exposed to these pesticides simultaneously or in quick succession.

How the pesticides might interact to disrupt normal cellular function:

- All three pesticides consume detox resources as part of their metabolism.
 - This results in DNA-damaging compounds being present in the cell for a longer time.
- The pesticides, their metabolites, and the compounds generated in 1a damage DNA.
- All three pesticides may attack:
 - Amino and sulfhydryl groups of DNA repair enzymes, impairing their ability to repair DNA damage.
 - The sulfhydryl groups of DNA methyltransferases, impairing their ability to control gene expression.



Cumulative Risk and Interactive Effects

Cumulative Risk: the risk associated with combined exposure to multiple chemicals. This could result from exposure to multiple chemicals at once (as with a product that is a mixture of multiple pesticides), or exposure to one chemical and later exposure to another chemical.^{iv}

Additive Effects: when chemicals target the same tissue or organ, the risks from each chemical are usually added to determine the cumulative risk.

Synergistic Effects: a type of *interactive effect* when exposures to two or more chemicals produce toxic effects that are **greater than the sum of its parts**. For example, if chemical A mutates DNA and chemical B disables a DNA repair enzyme, co-exposure to A and B would likely result in DNA mutation rates that are greater than additive, further increasing the risk of cancer. *Synergistic effects* impact the *cumulative risk* by making the health impact multiplicative rather than additive.

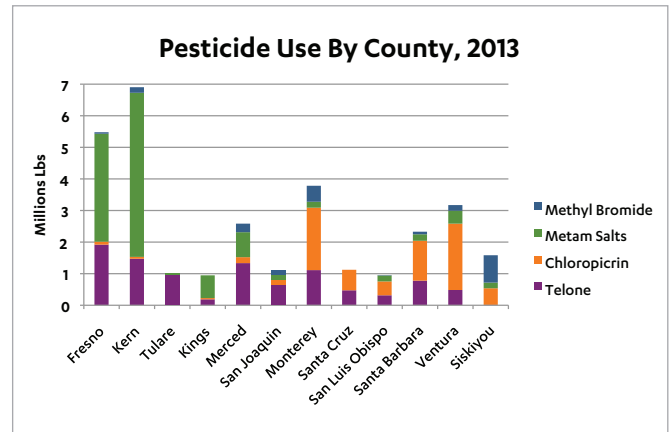
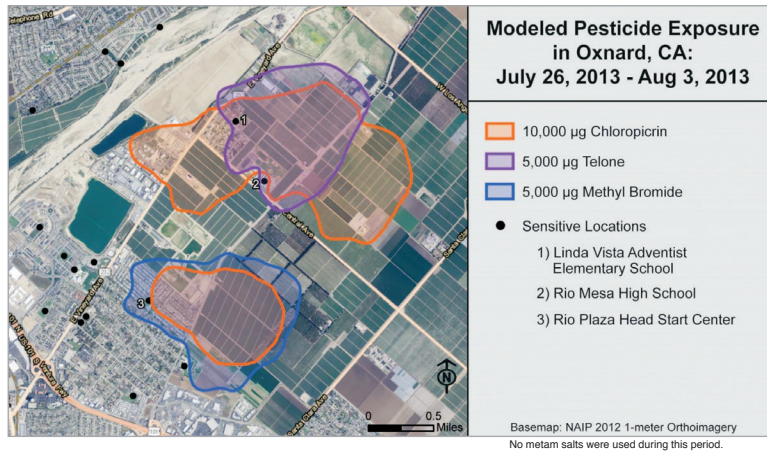
This summary focuses on possible *synergistic effects* and approaches for controlling them. Use of the three pesticides is likely to lead to additive increases in cumulative risk separate from synergistic effects, which are also largely ignored in pesticide regulation.

CALIFORNIANS ARE EXPOSED TO MULTIPLE FUMIGANTS

The three pesticides are applied in high volumes in some areas of California, and are often applied together or in close proximity to each other. In 2013 in California:

- ▶ There were 9,108 applications of chloropicrin, metam salts, dazomet, Telone, or methyl bromide
- ▶ 26% of these applications (12.11 million pounds) involved use of a product containing multiple active ingredients.
- ▶ 35% (2.64 million pounds) of fumigants were applied on the same day to the same field. The most common mixtures used were chloropicrin/methyl bromide and chloropicrin/Telone.

This study did not assess the health effects of methyl bromide because of its planned phase out. However, it was included in the exposure assessment because it was heavily used during the period analyzed.



The pesticides considered here are fumigants. This means they are usually vapors, and are likely to volatilize and drift away from the application site and expose people in surrounding schools, houses, businesses and fields. In fact, modeling shows that over the course of about one week people who live and work in the area around Rio Mesa High School in Ventura County were exposed to large doses of multiple fumigants. This level of exposure raises concerns about possible interactive effects, including glutathione depletion, increased rates of DNA mutation, and impeded DNA repair.

DPR CAN DO MORE TO PROTECT PEOPLE FROM INTERACTIVE EFFECTS

The regulatory system that is supposed to protect people from harmful levels of pesticide exposure has been slow to deal with interactive effects when setting exposure limits for pesticides. None of the possible interactive effects summarized in this report would be assessed under current approaches. **Under California law, DPR is required to consider a variety of human and environmental impacts,^v including cumulative impacts.^{vi}** While there is no silver bullet approach to dealing with interactive effects, this report recommends DPR do the following to more adequately protect human health:

- ▶ Some pesticides are sold as part of a mixture. These products should be tested for synergistic toxic effects before being approved for use.
- ▶ Pesticides are often (a) mixed with others for application at the site, (b) applied shortly after other pesticides, or (c) applied near other pesticides. Where there is a scientifically reasonable hypothesis of synergistic effects, regulators should either require testing or impose stringent restrictions to avoid the likelihood of health impacts.
- ▶ Synergistic effects of pesticides—occurring either because the pesticides are marketed in combination or because they are commonly used together—must be considered in the risk assessment and in establishing risk management requirements.

Modeling Exposure Near Rio Mesa High School

The exposure map above was generated using an EPA model of air dispersion with the following inputs:

- ▶ The type, amount, location, and timing of pesticide use in this area from July 26, 2013 through August 3, 2013. This information was gathered from the Ventura County Agricultural Commissioner's office.
- ▶ DPR established emissions ratings for each of the fumigants considered.
- ▶ Local terrain maps and meteorological data from local weather stations during the week in question.
- ▶ A list of local "receptors," i.e. sensitive locations like schools, day cares, and parks.

CONCLUSION

Interactive effects may increase health risks associated with exposure to multiple pesticides. Exposure data shows that Californians are regularly exposed to more than one of these pesticides simultaneously, and that low income and minority residents bear the greatest risk. DPR can and should do more to assess the risk of interactive effects associated with the use of multiple pesticides, and should take clear steps to protect residents.

This study focused on synergistic effects that would affect cancer potency. Interactive effects from these and other pesticides may also increase the risk of other human health problems, including those related to developmental, reproductive, and neurotoxicity, but such synergistic effects were not investigated in this report.

Assessing the interactive effects of pesticides will be complex. As society seeks to balance the human and environmental harm caused by pesticides with the economic benefits they provide, both the interactive effects and the costs of assessing them must be considered.

ADDITIONAL INFORMATION

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The **Full Report and Supporting Materials** are available at <http://www.stpp.ucla.edu/node/586>. This also includes links to interactive online maps showing pesticide use by township in select communities throughout California.

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ENDNOTES

- i Kocaman AY, Topaktaş M. 2010. Genotoxic effects of a particular mixture of acetamiprid and α -cypermethrin on chromosome aberration, sister chromatid exchange, and micronucleus formation in human peripheral blood lymphocytes. *Environ Toxicol* 25:157–168. doi:10.1002/tox.20485.
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- iv Risk Assessment of Combined Exposure to Multiple Chemicals: A WHO/IPCS framework WHO Supplement, *Regulatory Toxicology and Pharmacology*, Volume 60, Issue 2, Supplement, Pages S1-S14 (1 July 2011). Edited by M.E. Meek et al.
- v California Food and Agricultural Code. 1997. Section 12824.
- vi California Code of Regulations. 2014. Guidelines for Implementation of the California Environmental Quality Act, Section 15355.



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