Current State of the Science on Interactive Effects

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Outline

- Types of biological mechanisms that can produce interactions
- Likely interaction mechanisms for the soil fumigants
- Levels of combined exposure that could produce appreciable synergism
- Feasible laboratory studies that could verify and begin to quantify the potential for interactions

Types of biological mechanisms that can produce interactions

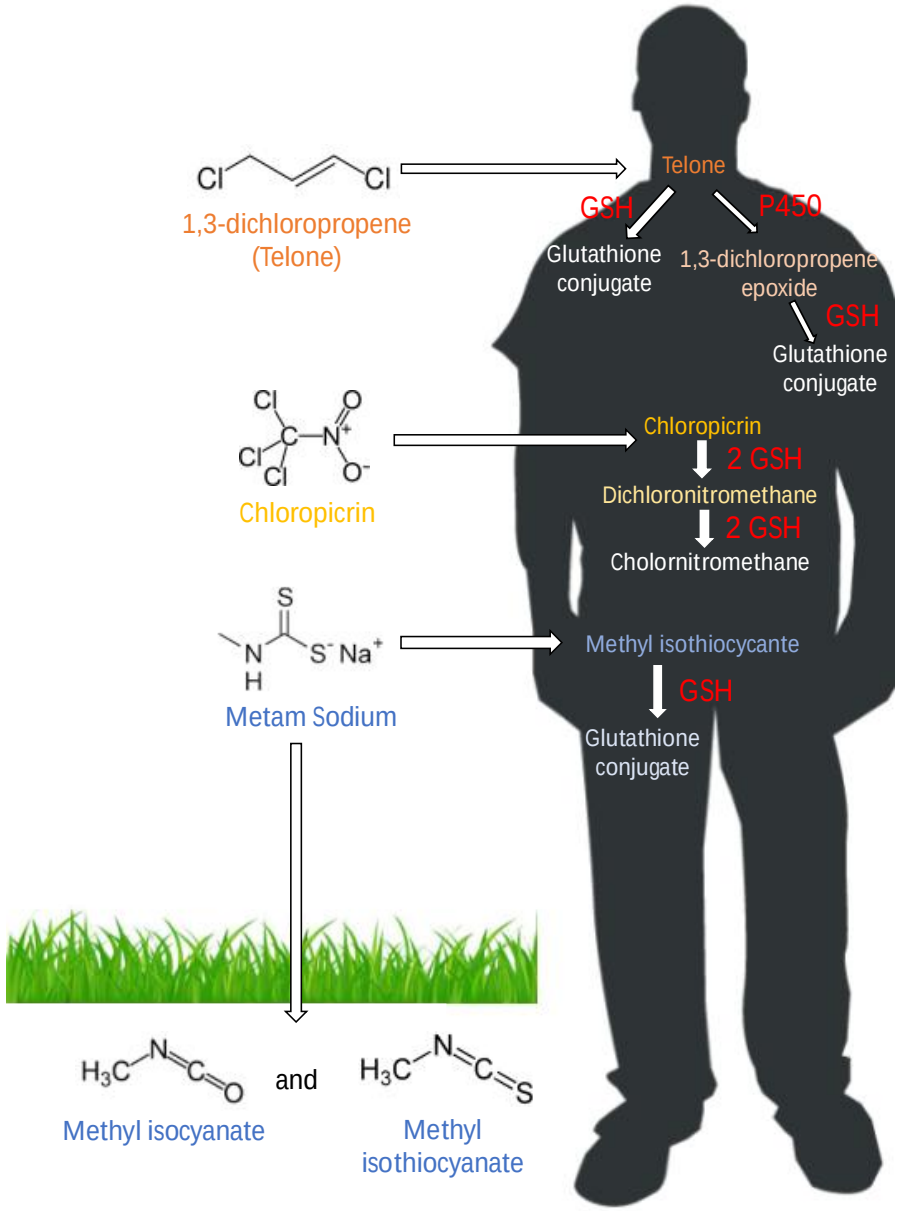
- Pharmacokinetic—One agent alters the uptake, metabolism, or elimination of another
- Pharmacodynamic—One agent alters the dynamics of the actual damage process of another at the site of toxic/carcinogenic action in the body

Pharmacokinetic Interactions

- Saturation of Active Transport Processes
- Inhibition of Metabolism—Lengthening Presence in the Body by Enzyme Inhibition or Depletion of Cofactors (e.g. Glutathione)
- Competition for Active Excretion or Resorption Processes

Pharmacodynamic Interactions

- Enhancement of Oxidative Stress Processes via Glutathione Depletion
- Inhibition of DNA Repair—Enhancement of the Persistence of DNA Lesions—e.g. via reactions with active-site sulfhydryls
- Toxicity-enhanced cell replication reduces the time available for DNA repair before a damaged DNA site is copied—enhancing mutations per DNA lesion
- Mutagenic Action at Different Stages in a Multi-stage Carcinogenic Process


1,3-dichloropropene
(Telone)
Telone
GSH
P450
Glutathione
conjugate
1,3-dichloropropene
epoxide
GSH
Glutathione
conjugate
Chloropicrin
Chloropicrin
2 GSH
Dichloronitromethane
2 GSH
Cholornitromethane
Metam Sodium
Methyl isothiocycante
GSH
Glutathione
conjugate
and
Methyl isocyanate
Methyl
isothiocyanate

Important New Non-Invasive Experimental Measurements of Glutathione Turnover In Vivo

(Skamarauskas et al. Hepatology 2014 59(6):2321-2330)

- Inject 13C-glycine to Animals or Humans, and Watch the Incorporation into the Plasma Pool of Glutathione and Specific Organs via Magnetic Resonance Imaging
- Provides Information on Susceptibility to Oxidative Stress or the Combined Effects Multiple Oxidative Stressors
- Knowing the Flux Allows Us to Calculate How Much of a Glutathione-Depleting Chemical Is Needed to Have How Much Effect on Internal Anti-Oxidation Capacity

Concentrations of the Individual Fumigants (ppm) Needed to Deplete 10% of the Whole Body Production of Gluathione for Select Demographic Groups

	Chlropicrin Needed (assuming 2 moles/mole GSH)	Chlropicrin Needed (assuming 4 moles/mole GSH)	Telone or metam sodium needed (assuming 1 mole/mole GSH)
Ave. adult, light activity	0.63	0.32	1.26
Ave. Adult, moderate activity	0.29	0.15	0.58
Adult with 95th %tile breathing rate, moderate activity	0.22	0.11	0.44
Elementary school children	0.34	0.17	0.68
Average infant, light activity	0.14	0.07	0.28
Infant, 90th %tile breathing rate, light activity	0.09	0.05	0.18

Likely Extent of Local Depletion of Glutathione in the Lung Depends on the Rate of Local Reaction vs Loss to the General Body Circulation

- In Addition to the Systemic Depletion Modeled Earlier, We Can Also Make Some Assessment of Potential Depletion of Lung Glutathione if Local Reaction Were Relatively Rapid Compared to Loss from the Lung with Blood Passing Through

Expected Percentage Reduction in Lung Glutathione if Nearly All Absorbed Chloropicrin Reacts Locally

ppm chloropicrin exposure

Time after start of exposure (hrs)	0.5	1	2	4
1	8%	15%	30%	60%
2	10%	19%	39%	77%
4	10%	21%	42%	84%
8	11%	21%	42%	85%

Other Examples of Plausible Interactions that Could be Assessed and Quantified Experimentally

- Enhancement of bladder carcinogenicity of telone by metam sodium—Bladder hyperplasia induced by metam sodium might affect the dose response for telone bladder tumor induction—requires chronic bioassay of rodents exposed to both agents
- Possible inhibition of DNA repair by electrophilic binding to active site sulfhydryl group—enhancing carcinogenesis by genotoxic carcinogenesis-–can be explored first by in vitro studies of inhibition of O6 alkylguanine transferase mediated repair activity by chloropicrin, metam sodium, or telone

Bottom Line

- In most cases, relatively modest additions to toxicological protocols could usefully help assess concerns for plausible interactive toxic effects.
- Imagination is needed to make plausible hypotheses about likely modes of interaction
- Determination is needed to bring about fair experimental assessment of these possibilities for application to risk assessment and regulatory safety decision-making.