how the tumors in the mouse intestinal study developed. This work has been fruitful. We now know that only chronic dietary exposures to very high doses of Captan irritate the intestine. This irritation sets off a chain of events that lead to increased cell-turnover and eventual promotion of previously quiescent pre-cancer cells to tumors. Each of these events is believed to occur at very high thresholds of exposure, below which no adverse cellular changes occur.

Is there a difference in tumor risk level for agricultural workers vs. consumers? No.

The risk to workers and consumers from oral exposure to Captan is the same – essentially **zero** – due to the exceptionally high Margin of Safety. The skin absorption risk for cancer or other systemic effects to workers (anyone who mixes, loads or applies Captan) also is essentially **zero** because of the very low rate of skin absorption coupled with the immediate degradation (under 7 seconds). The result is no systemic exposure, and without exposure there can be no adverse effects.

The Environmental Facts

Since Captan was introduced five decades ago in the U.S. and many countries throughout the world, there have been no reported adverse environmental effects associated with its use.

In its reregistration documents, the EPA notes: "For environmental fate concerns, Captan dissipates rapidly, with a half-life of less than one day, determined by hydrolysis and soil aerobic studies." Captan breaks down "moderately rapidly to rapidly" into its metabolites, which are not expected to persist in soil or surface water, and which degrade into carbon dioxide, inorganic sulfur and chlorine.

Captan was not detected at depths of 0-15 cm in either of two soil types one week after application as a drench, due to its rapid degradation. When used as directed, the sites and methods of use are not compatible for water or soil residue buildup.

Captan is nontoxic to bees, predatory or parasitic insects and mites. It is an excellent compound for Integrated Pest Management programs. Captan also has been shown to be relatively nontoxic to birds in dietary studies. The EPA states that "Captan is practically non-toxic to the Northern Bobwhite Quail and Mallard, on both an acute and subacute dietary basis." Similarly, Captan was described as practically non-toxic to small mammals on an acute oral basis.

Captan is moderately toxic to some freshwater invertebrates, and it is toxic to fish. However, there are no registered aquatic uses for Captan, so there is little likelihood of contamination of water resources. The aquatic toxicity of Captan via contamination of water bodies will be rapidly eliminated due to its fast degradation in water. The resulting degradates are practically non-toxic to aquatic organisms.

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When using agricultural chemicals, always read and follow label directions.

CAPTAN

Health and Safety

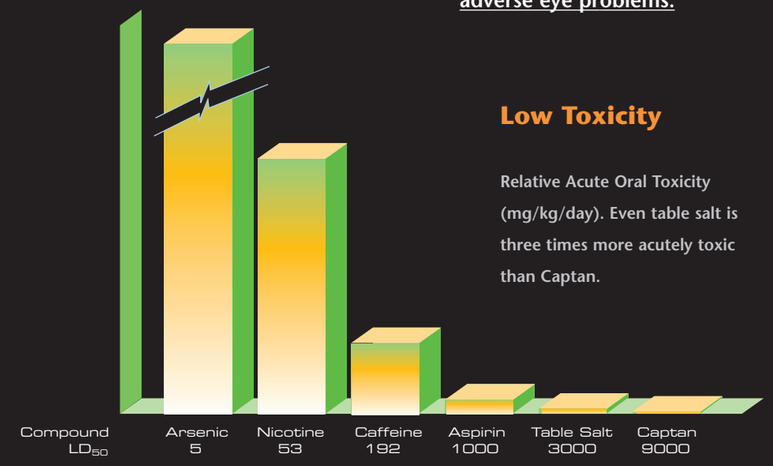
The Health and Environmental Facts Make Captan a Sound Choice.

New fungicide chemistries are commercialized each year, but Captan has been – and remains – the benchmark standard for crop disease protection. Unfortunately the messages that accompany some new products can be misleading, both about their own performance and about the health and safety characteristics of their competitors such as Captan.

We believe the facts about Captan – particularly its excellent human and environmental record, as well as its proven protection of yield – fully justify our continued trust in Captan to safely deliver its unparalleled crop disease control throughout the world.

During Captan's journey to receiving its Reregistraton Eligibility Decision (RED) from the U.S. Environmental Protection Agency, the following health and safety factors were among those examined.

- **The EPA classified Captan as a Class I compound [with a DANGER signal word] because it can be corrosive in the eyes, which is why eye protection always has been part of the regimen when working with Captan. In spite of this concern, Captan has been used for more than 50 years without reports in the scientific literature regarding adverse eye problems.**



Low Toxicity

Relative Acute Oral Toxicity (mg/kg/day). Even table salt is three times more acutely toxic than Captan.

- **Acute Oral LD_{50} is greater than 9,000 mg/kg. This level is considered "practically nontoxic." A lethal dose would require a person to swallow well over a pound of Captan in its technical compound strength.**

- **Acute Dermal LD_{50} is greater than 5,000 mg/kg. Captan does not readily penetrate the skin and is classified as "practically nontoxic" by skin exposure. In its RED, the EPA refers to Captan as "a moderate skin sensitizer." Clinical trials show the incidence of susceptible people to be very low, and actual field experience, particularly with strawberry workers, shows sensitization is not a problem. Anyone hypersensitive to Captan may experience itching, redness or a rash. Minor first-aid treatment and discontinuation of Captan exposure should clear up these skin problems.**

- **Acute Inhalation LC_{50} is 1.16 mg/L/4hr (nose only). Captan may cause irritation of mucous membranes, and as with any chemical the inhalation of dusts should be avoided.**

- Animal studies have shown that **Captan in the intact animal does not damage DNA, nor is it mutagenic.**

- Captan has been in many reproductive and developmental studies. It **does not cause birth defects, nor is it a developmental toxin.**

CAPTANFACT

During the reregistration eligibility process, the EPA reviewed the extensive Captan database of hundreds of studies, including many new scientific evaluations as well as those conducted over five decades of Captan use. The agency applied very conservative risk assessment standards before issuing the RED.

The database on Captan is more current and extensive than that of many other fungicides, both new and old. The data shows Captan meets regulatory standards applied to the newest fungicide technologies. Captan meets the rigorous standards of the Food Quality Protection Act children's sensitivity issue.

The EPA's documentation contains more than 110 citations referencing toxicology and exposure studies, and more than 80 citations referencing ecological and environmental studies. New studies were conducted and presented. EPA examined all the evidence.

Had there been any data or misgivings about the toxicology, food safety, or environmental activity of Captan, severe restrictions could have been imposed or the registration canceled. That did not happen.

The U.S. is not the only country where Captan has been investigated and its use continued. Germany and Australia recently renewed Captan registration after suspending it for several years to study the carcinogenicity issue. Captan continues to be registered in more than 50 countries, including 10 in the European Union where environmental and food safety organizations hold considerable power. Captan is used in Canada, Japan and Brazil as well.

A New Blood Study

A 1999 study of Captan in human blood is the latest in a series of dozens of such research programs over the decades. Scientists have known at least since 1967 that Captan breaks down rapidly when it comes into human blood. Just how fast that process happens was one of the most impressive results of the new study, which was conducted under stringent modern protocols so the data would better fit today's scientific standards.

The respected, independent Horizon Laboratories, Inc., of Columbia, Missouri, was asked by Makhteshim-Agan of North America, Inc. to conduct the study. Michael Williams, Ph.D., was Principal Analytical Investigator for the research.

The study measured the *in vitro* half-life of Captan in human whole blood at 37° C (98.6° F) and found it to be 0.97 seconds.

Scientists consider that absorbed materials are essentially eliminated from the body in seven half-lives. That means that in just 7 seconds any and all Captan that might pass through the skin is gone! It takes only a few half-lives to get down to one molecule, and then that also is gone. With a half-life under 1 second, even a "bolus dose" of a million molecules of Captan would disappear from human blood in approximately 21 seconds.

Through HPLC/mass spectrometry, THPI was found to be the sole, short-term degradate of Captan in whole blood. The EPA notes in its Captan reregistration documents that THPI (tetrahydrophthalimide) is not believed to contribute to carcinogenicity. This means that Captan breaks down in a matter of seconds into a substance that is not of toxicological concern.

An early study with mice fed very high doses of Captan for most of their lifetime resulted in some increased incidence of intestinal tumors in the mice. This has been interpreted by some to mean that a cancer risk to humans may exist. However, this is not the case. Research also shows that people exposed by the dermal or inhalation route during their work with Captan in agriculture have essentially no risk of developing intestinal tumors. First, Captan is absorbed only slowly from the skin. Secondly, Captan disappears from the blood in a few seconds.

It also is possible to calculate the level of risk of developing tumors from consuming produce with residues of Captan. This is done by figuring the threshold dose necessary for tumors and comparing that with the expected chronic exposure to residues.

The threshold for tumors in mice is above 60 mg per kg of body weight per day. This is the completely safe dose EPA uses as its benchmark. A Margin of Safety is calculated based on estimates of exposure. The benchmark exposure level EPA established for Captan is 0.00005 mg/kg/day. **This is a 1.2 million Margin of Safety!** Such an extraordinarily high safety margin is the basis for saying Captan presents essentially no risk to consumers.

Any route of exposure – oral, dermal or inhalation – is thus without risk for cancer. Statements to the contrary are inconsistent with research data.

Makhteshim-Agan has spearheaded research aimed at showing exactly

CAPTAN

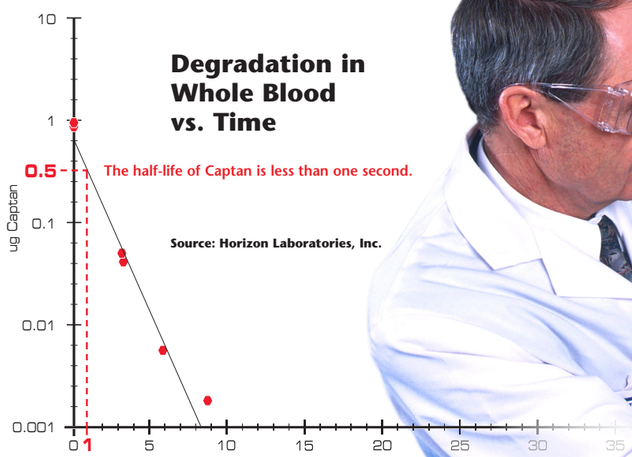


Photo courtesy of USDA