

● "INERT" INGREDIENT FACTSHEET

NONYL PHENOL AND RELATED CHEMICALS

Nonyl phenol and the related nonyl phenol ethoxylates are used in pesticide products as "inert" ingredients and as adjuvants added by the pesticide user.

Nonyl phenol is acutely toxic. Symptoms of exposure include eye and skin irritation, headaches, nausea, and death if enough exposure occurs. Nonyl phenol ethoxylates are also acutely toxic; the amount required to cause death is greater than with nonyl phenol.

Nonyl phenol and some of its ethoxylates are estrogenic; they mimic the action of the hormone estrogen. Nonyl phenol ethoxylates have been shown to reduce fertility in laboratory animals.

Nonyl phenol and some of its ethoxylates cause breast cancer cells to increase in number.

Nonyl phenol and its ethoxylates are acutely toxic to a wide variety of animals: bees, spiders, fish, molluscs, and crustaceans. Sublethal effects include reduced fertility, irregular heart beat, and loss of normal movements. Nonyl phenol bioaccumulates in aquatic organisms.

Nonyl phenol inhibits seed germination in some plants. It also inhibits the growth of aquatic plants and algae.

Nonyl phenol has persisted in soil for almost a year.

BY CAROLINE COX

Nonyl phenol and related compounds (see Figure 1) are used as surfactants (surface-active agents). Surfactants reduce the surface tension of water¹ and form a bridge between two chemicals that don't readily mix.² They are used in pesticide products as "inert" ingredients (ingredients other than the named, active, pesticidal ingredient). They are used to increase the amount of a spray solution that remains on leaf surfaces, to make the spray droplets stick better to the leaf, and in general make the pesticide product more potent.³

Introducing this
Chemical Family

Nonyl phenol is not a single chemical compound. Instead, the term is used to refer to a family of compounds all of which have a central aromatic (or benzene) ring and a nine carbon side chain. (See Figure

1.) 4-nonyl phenol, in which the side chain is attached to the carbon directly opposite the hydroxyl group (OH; an oxygen and a hydrogen atom) is the most common member of this family, making up over 90 percent of commercial nonyl phenol.⁴ In addition, the nine carbon side chain can have many different shapes; a branched side chain is more common than a side chain with all nine carbons in a straight line.⁵ Similar compounds with side chains with different numbers of carbon atoms are grouped together as alkyl phenols.

Surfactants related to nonyl phenol but with additional groups of atoms called ethylene oxide units are called nonyl phenol ethoxylates. (See Figure 2.) Alkyl phenol ethoxylates is another commonly-used term used to group the nonyl phenol ethoxylates with some closely related compounds that have carbon side chains of different lengths.

Once released into the environment, nonyl phenol ethoxylates break down into nonyl phenol, nonyl phenol monoethoxylate, nonyl phenol diethoxylate, (see Figure 2), and other related compounds. These breakdown products are called

"biorefractory" because they are persistent in the environment.⁶ Therefore, this article discusses the toxicology of all of these compounds, with primary emphasis on nonyl phenol.

Nonyl phenol ethoxylates are also widely used as surfactants in industrial and institutional cleaning products.⁷ This article will not focus on these uses.

Estimated Use

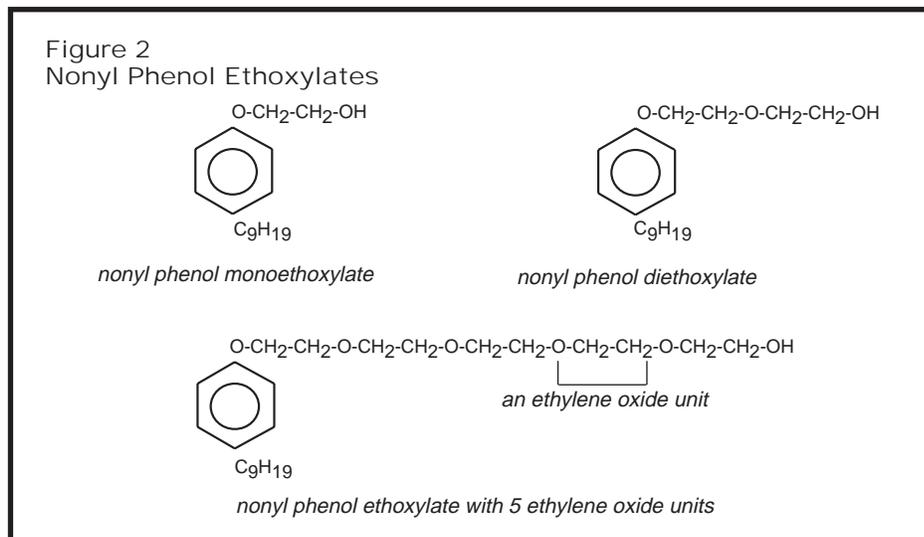
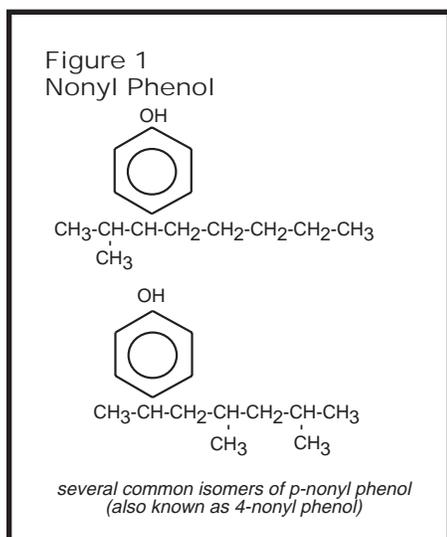
Nonyl phenol is classified by the U.S. Environmental Protection Agency as an "inert of toxicological concern" that must be identified on pesticide labels.⁸ Because of this, the names of the pesticide products containing nonyl phenol are publicly available: 5 formulations of Vinyzene (a preservative and fungicide), 4 formulations of Nytek, 2 formulations of Socci, and Cunilate (all three are wood preservatives).⁹

Nonyl phenol ethoxylates are claimed as trade secrets when they are used as "inerts." Therefore, it is difficult to estimate how much of these surfactants are used, or in how many products.

The best publicly available estimates in-



Caroline Cox is JPR's editor.



dicates that they are used widely. All of these chemicals belong to a class of surfactants called nonionic surfactants, which “are an integral part of the majority”³ of pesticide products. Alkyl phenol ethoxylates, together with another class of surfactants called alcohol ethoxylates, are the two “largest classes of nonionic surfactants in current use.”⁸ About 80 percent of alkyl phenol ethoxylates are nonyl phenol ethoxylates; the other 20 percent are octyl phenol ethoxylates, a very similar class of compounds with an eight (rather than nine) carbon side chain.¹⁰ Overall, agricultural chemicals are the third largest industrial use of alkyl phenol ethoxylates in the U.S.¹¹

Alkyl phenol ethoxylates are also used as pesticide adjuvants, products that are added to spray mixtures by pesticide users to make the pesticide product perform better. In California, a state with relatively comprehensive pesticide use reporting, pesticide users must also report the use of adjuvants. Use of adjuvants that contain nonyl phenol ethoxylates totals over 1.5 million pounds per year. (See Figure 3.) Adjuvants added to pesticides used on rights of way, cotton, grapes, almonds, and nectarines account for the majority of the alkyl phenol ethoxylates used in California.¹²

Acute Toxicity

Nonyl phenol is acutely toxic; short term exposures cause immediate adverse effects. Important problems include the following:

Acute Toxicity to Humans: Exposure to nonyl phenol if swallowed, inhaled, or absorbed through skin causes severe irritation. High concentrations are extremely destructive to the upper respiratory tract, eyes, and skin. Symptoms of exposure include coughing, wheezing, a hoarse voice, shortness of breath, headache, nausea, and vomiting.¹³

Mortality: The amount of nonyl phenol that causes death of laboratory animals is highly variable. For rats, the median lethal dose (LD₅₀; the amount that kills 50 percent of a population of test animals) varies from 400 milligrams per kilogram (mg/kg) of body weight to 1620 mg/kg of body weight.⁴ Nonyl phenol ethoxylates are less acutely toxic; the lowest LD₅₀ reported for rats was 1650 mg/kg of body weight.¹⁰

Dermal Exposure: Prolonged contact of nonyl phenol with skin causes burns, irritation, and swelling.⁴ When applied to the skin of rabbits, it has caused skin tissue to decay; additional symptoms included diarrhea, lung and liver congestion, and mottled kidneys. Nonyl phenol has been characterized as “severely irritating” while ethoxylates with 2 to 9 ethylene oxide units are “moderately to severely irritating.” When nonyl phenol is applied to the skin of guinea pigs several times, later applications will have a more intense response than the first; this is called a sensitization response.^{4,14}

Eyes: A small amount (less than a thousandth of a milliliter) of nonyl phenol causes

immediate severe eye irritation in rabbits.⁴ Texaco Chemical Company warns that damage may be permanent.¹⁰ Undiluted nonyl phenol ethoxylates are severely irritating; 10 percent solutions are moderately to severely irritating.¹⁰

Other Acute Toxicity: Both nonyl phenol and nonyl phenol ethoxylates inhibit one of the reactions (reverse electron transfer) that occur inside a cell to extract energy from food.¹⁵ Nonyl phenol also inhibits the activity of an enzyme (ATPase) that is important in the process of providing energy to muscle cells.¹⁶

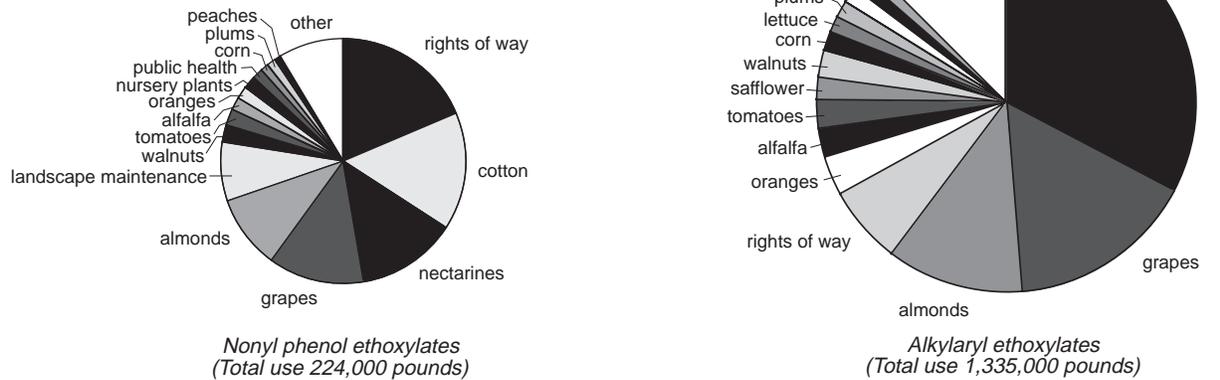
Effects on the Circulatory System

Feeding dogs nonyl phenol ethoxylates with between 17 and 20 ethylene oxide units for 90 days caused spots of dead tissue to develop on the heart muscle tissue. In cats, nonyl phenol ethoxylate with 20 ethylene oxide units caused the heart muscle not to contract normally.¹⁰

Effects on Reproduction

Nonyl phenol ethoxylates cause reproductive problems in laboratory animals. Problems caused by the ethoxylate with 9 ethylene oxide units include inflammation of the vagina in rabbits; inflammation of the vagina followed by stretching of the uterus in rats; a reduction in the number of viable embryos in rats; and a reduction in the number of successfully implanted em-

Figure 3
Use of Adjuvants Chemically Related to Nonyl Phenol in California (1993)



Source: California Environmental Protection Agency. Dept. of Pesticide Regulation. Information Services Branch. 1995. Pesticide use report: Annual 1993. Indexed by chemical. Sacramento, CA. (June.)

Use of pesticide adjuvants related to nonyl phenol totals over 1.5 million pounds annually in California. This chart shows use of the two types of adjuvants containing nonyl phenol ethoxylates tabulated by the California Department of Pesticide Regulation (DPR). The right pie chart shows use of alkylaryl ethoxylates, adjuvants that contain a mixture of surfactants including nonyl phenol ethoxylates that DPR was not able to identify more specifically. The left pie chart shows use of adjuvants identified specifically as nonyl phenol ethoxylates.

bryos in rats along with an increase in endometriosis,¹⁷ a disease in which uterus lining cells grow at sites outside of the uterus.¹⁷

In addition, nonyl phenol and related compounds affect reproduction because they are estrogenic. This means they mimic estrogens, hormones that are responsible for the development and maintenance of secondary sexual characteristics and behavior. Estrogen mimics disrupt the normal functioning of the hormone system, leading to potential reproductive problems. Although the first demonstration that alkyl phenols were estrogenic was published in 1978,¹⁸ it is only recently that these estrogenic effects have received significant publicity.¹⁹

Different kinds of studies show that nonyl phenol is estrogenic. For example, nonyl phenol and related compounds bind to the estrogen receptor, a specific protein found inside cells that respond to estrogen. The estrogen-estrogen receptor complex then activates that part of the genetic material concerned with cell division.²⁰ Nonyl phenol is less potent at binding to the estrogen receptor than natural estrogens and octyl phenol, but more potent than nonyl phenol carboxylic acid.⁹ Nonyl phenol also

caused increased cell division in the lining of the rat uterus,¹⁹ and caused enlargement of the uterus in juvenile rats.²¹ Both are typical estrogen-like actions.

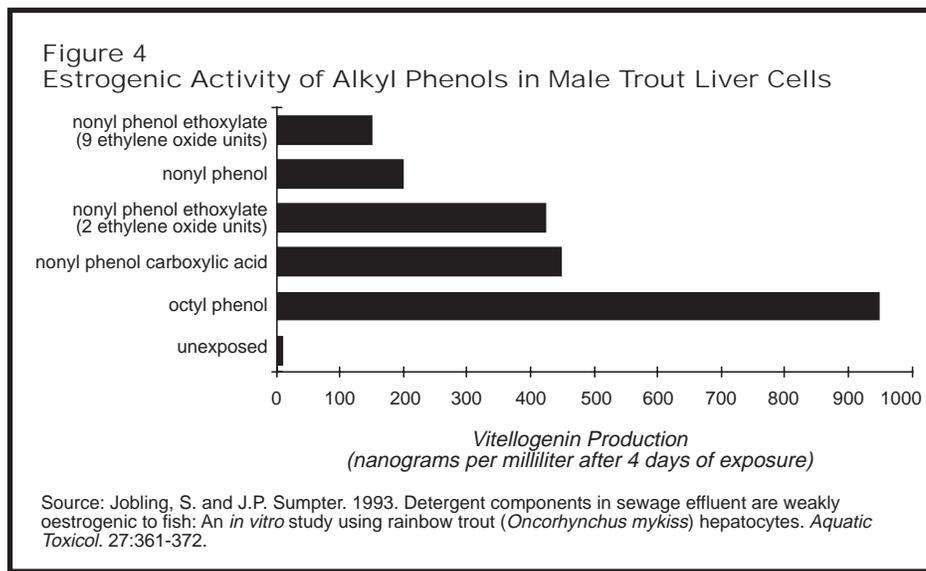
“The sperm production of some of the offspring of octyl phenol-exposed mothers was measured; it was between 10 and 20 percent less than that of unexposed rats.”

Exactly how estrogenic chemicals, like nonyl phenol, affect the whole process of reproduction is only just beginning to be understood. A recent study of octyl phenol and octyl phenol ethoxylate points out the kinds of problems that exposure to these compounds can cause.²² In this study, mother rats were fed octyl phenol (or the ethoxylate) throughout their pregnancies

and during the time they were nursing. When their offspring reached adulthood, the males had smaller testes, both in absolute terms and relative to their body weight. The sperm production of some of the offspring of octyl phenol-exposed mothers was measured; it was between 10 and 20 percent less than that of unexposed rats. The study was striking because the exposure was all through the mothers and the amounts of octyl phenol which the mothers consumed was small, between 0.1 and 0.4 mg/kg of body weight per day. Nonyl phenol is likely to have similar effects, though in higher amounts because it is not as potent an estrogen mimic as octyl phenol.

Carcinogenicity

Nonyl phenol's ability to mimic estrogen causes concern about its ability to cause cancer because some cancers (most notably certain common breast cancers) are associated with estrogen exposure. Nonyl phenol and related compounds have been tested for this kind of effect by testing them in human breast cancer cell cultures. In this test, estrogen and estrogen mimics will cause cell proliferation, an increase in the number of cells in the culture. Octyl phenol,



Nonyl phenol and related compounds mimic the hormone estrogen in fish. This estrogenicity is measured by how much the production of vitellogenin, a protein used in the yolk of the fish eggs, is increased.

nonyl phenol, nonyl phenol diethoxylate, and nonyl phenol carboxylic acid all caused cell proliferation; octyl phenol was the most potent.^{9,23}

Nonyl phenol ethoxylates are cocarcinogens; they increase the cancer-causing effects of other chemicals known to cause cancer. Rats whose drinking water contained the carcinogen MNNG (N-methyl-N'-nitro-N-nitroso guanidine) and nonyl phenol ethoxylate developed more stomach cancer and intestinal tumors than rats drinking water with MNNG alone.¹⁰

Mutagenicity

While many tests of alkyl phenol ethoxylates' ability to cause genetic damage have been negative, octyl phenol ethoxylate and nonyl phenol ethoxylate (both with 9 ethylene oxide units) have each caused genetic damage in one of the many types of tests used to screen for this kind of effect.¹⁰

Effects on Animals

Beneficial arthropods: Nonyl phenol is toxic to both spiders and bees, arthropods that are economically important because they kill unwanted insects and pollinate crops respectively. A Canadian study applied nonyl phenol to a forest at rates equivalent to those found after use of a forestry insecticide with nonyl phenol as an

"inert" ingredient. Mortality of spiders was five times that of untreated plots, and mortality of honey bees increased four-fold.²⁴

Aquatic Invertebrates: The acute and chronic toxicity of nonyl phenol to water fleas (*Daphnia*) is significant. Concentrations of about 0.2 parts per million (ppm) cause mortality. Chronic effects have been measured at concentrations about five times less; 0.04 ppm caused decreases in the number of offspring.²⁵ A nonyl phenol ethoxylate with nine ethylene oxide units was also toxic to water fleas, but at a higher concentration, 3 ppm.²⁶

Fish: Nonyl phenol is acutely toxic to fish, and relatively low concentrations can cause death. During the 1980s, researchers studying the use of the insecticide aminocarb to kill spruce budworm in Canadian forests were struck that "nonyl phenol [used as an adjuvant with the aminocarb] is considerable more toxic to certain aquatic species" than the aminocarb itself.⁴

The median lethal concentration (LC₅₀; the concentration in water that kills 50 percent of a population of test animals) for Atlantic salmon²⁷ and fathead minnows²⁸ is between 0.1 and 0.2 ppm. At a somewhat higher concentration (1 ppm), nonyl phenol kills rainbow trout eggs.⁴

Nonyl phenol ethoxylates are also toxic to fish. The LC₅₀ for fathead minnows is

1.6 ppm (9 ethylene oxide units),²⁶ for cod is 2.5-6 ppm, (10 ethylene oxide units)²⁹ and for rainbow trout is 8.5 ppm (9.5 ethylene oxide units).³⁰ LC₅₀s for other fish are similar. In general, ethoxylates with a small number of ethylene oxide units tend to be most toxic, and juveniles are more susceptible than adults.¹⁰ Fish gills are particularly sensitive to the presence of surfactants, and several studies have documented the destruction and marked deterioration of gills exposed to nonyl phenol ethoxylates.^{31,32}

Nonyl phenol is estrogenic in fish. This has been demonstrated by measuring the production of vitellogenin, a component of the yolk of a fish egg. Vitellogenin is produced by fish livers in response to estrogens. Males will produce vitellogenin if exposed to estrogenic chemicals. Using cultures of liver cells from male rainbow trout, researchers showed that octyl phenol, nonyl phenol, nonyl phenol carboxylic acid, and some nonyl phenol ethoxylates were estrogenic.³³ (See Figure 4.) A follow up study showed that trout exposed to sewer effluent produced from 500 to 100,000 times as much vitellogenin as unexposed fish.³⁴ The researchers later concluded that alkyl phenols in the sewer effluent were the likely cause.⁹

Most recently, the same researchers studied male fish living in water contaminated with alkyl phenols. Nonyl phenol increased vitellogenin production at concentrations of 10 ppb, while octyl phenol was active at even lower concentrations (3 ppb). Living in water with just 50 ppb of nonyl phenol caused a decrease in the size of the trout's testes. These concentrations are much lower than those that caused effects in the earlier cell culture tests.³⁵

Marine animals: Nonyl phenol is acutely toxic to marine animals other than fish. For lobster, the LC₅₀ is 0.2 ppm;⁴ and for sand shrimp the LC₅₀ is 0.3-0.4 ppm.³⁶ Nonyl phenol ethoxylates (with 10 ethylene oxide units) are acutely toxic to mussels (LC₅₀ 12 ppm), clams (LC₅₀ 18 ppm), barnacle larvae (LC₅₀ 1.5 ppm), hermit crabs (LC₅₀ 100 ppm) and spider crab larvae (LC₅₀ 10 ppm).²⁹ A nonyl phenol ethoxylate with nine ethylene oxide units caused mortality of shrimp at concentrations of 1.2 ppm.³⁷

Sublethal effects noted in these animals were irregular heartbeat in mussels, inability to burrow and to retract the siphon in clams, avoidance reactions in shrimp, and inability to swim in barnacle larvae.²⁹

Bioaccumulation: Concern about these adverse effects of nonyl phenol and its ethoxylates increases because these compounds bioaccumulate in algae,³⁸ mussels, shrimp,³⁹ fish, and ducks.³⁸ This means that concentrations are higher in these plants and animals than they are in the water in which the plant or animal lives. The bioconcentration factor (BCF) is used to measure how much bioaccumulation has occurred. It is calculated by dividing the concentration of nonyl phenol in the animal or plant tissue by the concentration in water. BCFs as high as 10,000 have been measured in algae.³⁸ In fish they vary between 3 and 1300,^{38,39} and BCFs for mallard duck³⁸ were similar to those measured in fish. BCFs of nonyl phenol ethoxylates were slightly lower, with values as high as 5,000 in algae and up to 300 in fish.³⁸

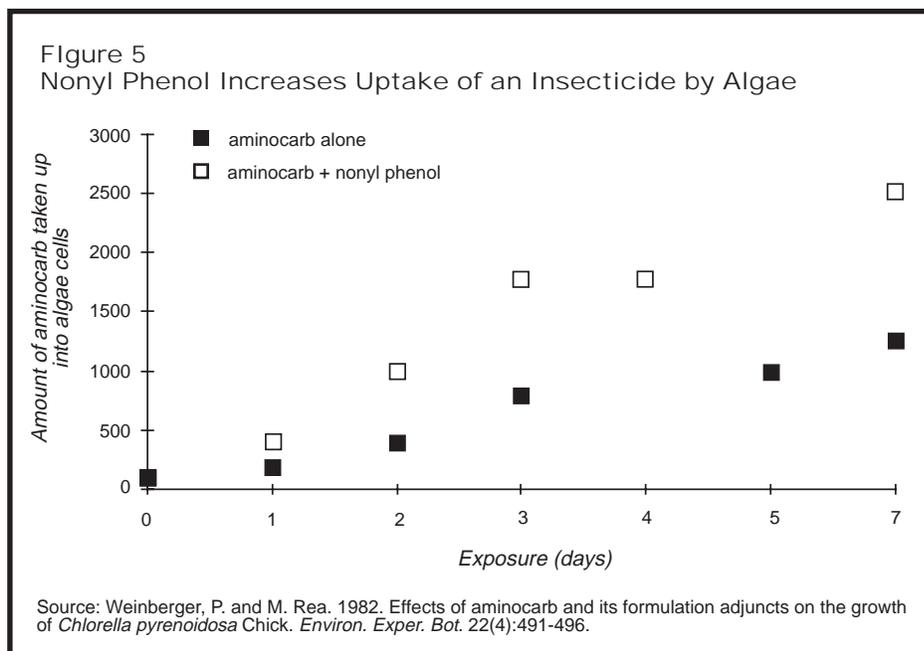
Effects on Plants

Trees: Nonyl phenol reduced the germination of both jack pine and white birch. In seedlings that successfully germinated, water uptake was reduced in jack pine, and sprout length was reduced in both species.⁴⁰

Crop plants/fruits: One treatment with a high concentration of a nonyl phenol ethoxylate with 5 ethylene oxide units caused a delay in bud break and up to 50 percent bud kill in apples. Peaches and grapes had similar symptoms.¹⁰ Nonyl phenol ethoxylates also caused damage to the leaves of kohlrabi. Highest damage was caused by ethoxylates with between 10 and 14 ethylene oxide units.⁴¹ In tissue cultures of sugarbeets⁴² and tomatoes⁴³, nonyl phenol stops or slows growth.

Aquatic plants: Nonyl phenol at concentrations below 1 ppm inhibited growth and caused a loss of chlorophyll in duckweed (*Lemna minor*). In the aquatic fern *Salvinia molesta*, concentrations of 2.5 ppm reduced frond production and caused death. In both of these plants chloroplasts (the site of photosynthesis) were damaged.⁴⁴

Algae: Nonyl phenol causes a variety of



When nonyl phenol is mixed with a pesticide chemical, it increases the amount of the pesticide that is taken up by algae cells. Because algae are used as food by animals, particularly juvenile fish, their exposure to the pesticide will increase as a result.

adverse effects to algae. Photosynthesis is suppressed in one species by concentrations of 0.5 ppm.⁴⁵ 2.5 ppm inhibited cell division in another species.⁴⁶ In a third species, 7.5 ppm delayed growth.⁴⁷ In late spring, algae are an important food resource for fish fry, so impacts on algae could have effects higher up the food chain.⁴⁵ For example, researchers point out that the third species of algae mentioned above is "at the base of the majority of the food chains of the organisms in these [forest] habitats."⁴⁷

Persistence in Soil

Since persistence in soil varies depending on climate, soil type and other factors, it is difficult to generalize about how long nonyl phenol and its ethoxylates persist. In a study of pasture soil amended with sewer sludge concentrations of nonyl phenol, nonyl phenol monoethoxylate, and nonyl phenol diethoxylate declined about 80 percent during the first month of the study; however, residues were still detected at the end of the study, 322 days after the first measurements were made.⁴⁸

Contamination of Water

Nonyl phenol and its ethoxylates are fre-

quently found in water, though it is difficult to identify contamination resulting from just pesticide-related uses.

In a sample of New Jersey drinking water, seven nonyl phenol ethoxylates were found with a total concentration of 725 parts per trillion (ppt). In addition, over 225 ppt nonyl phenol carboxylates and over 175 ppt of octyl phenol ethoxylates and carboxylates were found.⁴⁹

In a nationwide sampling of rivers with industrial or sewer effluent, 30 percent contained nonyl phenol, 33 percent contained nonyl phenol monoethoxylate, 42 percent contained nonyl phenol diethoxylate, and 24 percent contained ethoxylates with more ethylene oxide units. The highest concentrations measured were about 1 part per billion (ppb) for the first three compounds and 15 ppb for the fourth. In sediment samples taken from the same rivers, 72 percent of the samples contained nonyl phenol and 56 percent contained nonyl phenol monoethoxylate. The highest concentrations measured were 3000 ppb for nonyl phenol and 170 ppb for nonyl phenol monoethoxylate.⁵⁰

A similar study of river sediment in Florida which included rivers near pesti-

cide application sites found alkyl phenols in about 40 percent of the samples tested.⁵¹

After forestry insecticide spraying, residues of nonyl phenol persisted for five days in an Ontario, Canada stream.⁵²

Synergism

One of the most potentially troubling problems with "inert" ingredients in pesticide products is their potential to act synergistically with the other ingredients in the pesticide product. If two chemicals are synergistic, they will be more potent together than the sum of their individual potencies. For example, nonyl phenol increases the speed and the amount of the insecticide aminocarb that is taken up by algae. (See Figure 5.) The aminocarb then persists in the algae for between three and four times longer than it would persist in water. Fish eating the algae are thus exposed to aminocarb with nonyl phenol for much longer than they would be exposed to aminocarb alone.⁴⁷ ✦

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