Amazing Organohalogens

Although best known as synthetic toxicants, thousands of halogen compounds are, in fact, part of our natural environment

Gordon W. Gribble

The synthetic, chlorine-containing chemicals DDT (dichlorodiphenyltrichloroethane), dioxin, PCB (polychlorinated biphenyl) and CFC (chlorofluorocarbon) are persistent pollutants in our environment. Less well known—even to many scientists—is that nature produces an abundance of similar, and in some cases identical, halogenated compounds, some of which predate the beginning of life on Earth.

From simple, ubiquitous methyl chloride to the elaborate, chlorine-containing antibiotic vancomycin, nature creates halocarbons with a variety and structural complexity that human chemists cannot match. Chemists have tabulated 2,320 unique, naturally occurring organochlorines, along with 2,050 organobromines, 115 organoiodines and 34 organofluorines. Bacteria, fungi, plants and animals—including people—all produce halocarbons. They are also formed abiotically by forest fires, volcanoes and other geothermal events. In some instances, the natural compounds are precisely the same chemicals that are synthesized for industrial use. Yet the idea that nature produces halogenated molecules has struggled for recognition because of the potent toxicity of (and widespread publicity about) industrial creations such as chlorinated pesticides.

The emergence of bioprospecting—scouring the living world for useful organic compounds—has led chemists to hundreds of biosynthesized molecules that contain atoms of chlorine and bromine. This search has been catalyzed by SCUBA (Self-Contained Underwater Breathing Apparatus) technology, which has opened more of the ocean to exploration. Marine organisms are the richest sources for halocarbons—not surprising considering the high chloride and bromide content of seawater. Even the "smell of the ocean" is probably caused in part by volatile organohalogens from seaweeds. Some of these compounds, including methyl bromide, methyl iodide and bromoform, are also used by the chemical industry as pesticides or synthetic intermediates. But most organohalogens are new to science and have never been synthesized by people. For the species that make them, they serve as repellents and antifeedants, antibacterial and antifouling agents, pheromones and hormones.

Halo-whats?

A halogen (or "salt-former") is an element that has seven outer electrons—one shy of the number needed to complete the valence shell and lend stability to the atom. The potential payoff for that last electron—relaxation into a lower-energy state—is considerable, so halogens tend to be aggressive in getting it. Chemists describe this propensity as a large, negative, electron affinity, and it makes halogens combine readily with other elements. The common seven-electron configuration is reflected in a columnar arrangement on the Periodic Table. Of the five elements in the group, fluorine (F), chlorine (Cl), bromine (Br) and iodine (I) are used in biological molecules. The last and largest halogen, astatine (At), is radioactively unstable and not found in nature.

In their pure forms, these so-called Group VII elements exist as diatomic molecules, such as F_2 (diatomic fluorine) or Cl_2 (diatomic chlorine); both gases are quite reactive. Halogens tend to form ionic compounds with metals and covalent compounds with nonmetals. Examples of the former include most halides, such as sodium chloride; the latter include most carbon-containing, or *organohalogen,* molecules.

Bounty of the Sea

Sponges, corals and most seaweeds, being anchored to the reef, share an inability to evade predators and parasites. Lacking other means of defense, these organisms rely on chemical warfare for survival and are prodigal creators of halocarbon compounds. Among the sponge's weapons are several brominated dioxins, analogues of the infamous industrial dioxins, and numerous metabolites that prevent overgrowth by barnacles, thereby solving a problem that continues to afflict ships, piers and almost every other man-made object in the ocean. In Hawaii, "swimmer's itch" is caused by a bromine-containing seaweed compound, and limu kohu—the favorite edible seaweed of native Hawaiians—contains at least 100 organohalogens, nearly all of which have previously unknown chemical structures.

Figure 1. Organohalogen chemicals are often believed to be solely industrial compounds, but many living organisms and geological phenomena also produce them naturally. Volcanoes, such as the Uzon caldera in Russian Siberia *(right)*, can emit inorganic and organic halogenated gases, including methyl halides, chloroform, carbon tetrachloride and chlorofluorocarbons, during quiescent periods as well as during eruptions.

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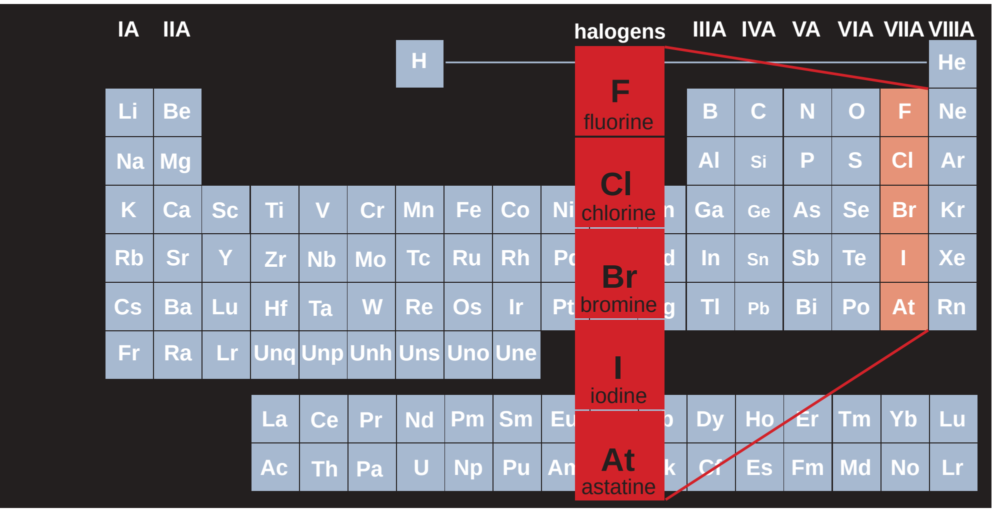
Nudibranchs and sea hares, two varieties of shell-less saltwater slugs, also depend on chemicals for survival in a world of predators. One species of sea hare secretes a bitter-tasting, bromine-containing metabolite called panacene to discourage prospective diners, including sharks. However, some nudibranchs lack the ability (or inclination—giving new meaning to the term "lazy slug") to synthesize their chemical arsenal, which is acquired instead from their diet of sponges or algae. In this case, bioaccumulation of noxious compounds in the food chain serves a specific and, for the slugs, a desirable purpose.

Other instances may be less benign. The discovery of halogenated bipyrroles in ocean-feeding seabirds (gulls, albatross, puffins, eagles) was the first example of a natural organohalogen, probably originating in a marine bacterium, to build up in top-level predators. A related compound called Q1 has been discovered in a myriad of marine consumers, including seals, dolphins, and the milk of Faroe Island women who eat whale blubber. These natural substances resemble anthropogenic PCBs, once used in electrical transformers and capacitors, in their chemical structure and propensity to concentrate at the top of the food chain. Although the pernicious properties of synthetic PCBs are widely known, the effects of Q1 and other natural halocarbons on the health of higher-order consumers are still being explored.

Passive Aggressive

Although not as prolific as their aquatic cousins, terrestrial plants and fungi also produce a multitude of chlorine-, bromine- and a few fluorine-containing chemicals. The simplest organobromine compound, methyl bromide (also called bromomethane), is a commercial fumigant and pesticide. It was recently banned in California because of its powerful ozone-depleting activity. But this chemical is also biosynthesized by members of the *Brassicaceae* family, which includes cabbage, broccoli, turnips and rapeseed (canola). The



compound name	formula	halogen	industry	nature
fluorine gas	F_2	F	yes	yes
fluoroacetic acid	$C_2H_3O_2F$	F	yes	yes
hydrogen fluoride	HF	F	yes	yes
tetrafluoroethylene	C_2F_4	F	yes	yes
CFC-11	CCl_3F	F, Cl	yes	yes
2,4-dichlorophenol	$C_6H_4OCl_2$	Cl	yes	yes
2,6-dichlorophenol	$C_6H_4OCl_2$	Cl		yes
carbon tetrachloride	CCl_4	Cl	yes	yes
chlorine gas	Cl_2	Cl	yes	yes
chloroacetic acid	$C_2H_3O_2Cl$	Cl	yes	yes
chloroform	$CHCl_3$	Cl	yes	yes
chlorophenol	C_6H_5OCl	Cl	yes	yes
cryptophycin 1	$C_{35}H_{43}N_2O_8Cl$	Cl		yes
DDT (1,1,1-trichloro-2,2-bis-(p-chlorophenyl) ethane)	$C_{14}H_9Cl_5$	Cl	yes	
dichloromethane	CH_2Cl_2	Cl	yes	yes
dioxin (ex., 1,3,6,8-tetrachlorodibenzo-p-dioxin)	$C_{12}H_4O_2Cl_2$	Cl	yes	yes
epibatidine	$C_{11}H_{13}N_2Cl$	Cl		yes
hydrogen chloride	HCl	Cl	yes	yes
hypochlorous acid	HClO	Cl	yes	yes
lindane	$C_6H_6Cl_6$	Cl	yes	
maracen A		Cl		yes
methyl chloride	CH_3Cl	Cl	yes	yes
PCB (polychlorinated biphenyl, ex., 2,2',4,4',5,5'-hexachlorobiphenyl)	$C_{12}H_4Cl_6$	Cl	yes	
punaglandin 1	$C_{27}H_{37}O_{10}Cl$	Cl		yes
Q1	$C_9H_3N_2Cl_7$	Cl		yes
spongistatin 9	$C_{61}H_{91}O_{20}Cl$	Cl		yes
vancomycin	$C_{66}H_{75}N_9O_{24}Cl_2$	Cl		yes
kalihinol A (prevents barnacle growth)	$C_{22}H_{33}N_2O_2Cl$	Cl		yes
telfairine	$C_{10}H_{14}Cl_3Br$	Cl, Br		yes
brominated dioxins (ex., 1-hydroxy-3,4,6,8-tetrabromodibenzo-p-dioxin)	$C_{12}H_4O_3Br_4$	Br		yes
bromoform	$CHBr_3$	Br	yes	yes
methyl bromide	CH_3Br	Br	yes	yes
panacene	$C_{15}H_{15}O_2Br$	Br		yes
aplysiatoxin (swimmer's itch compound)	$C_{32}H_{47}O_{10}Br$	Br		yes
methyl iodide	CH_3I	I	yes	yes
thyroxine	$C_{15}H_{11}NO_4I_4$	I		yes

Figure 2. Halogens are elements with seven outermost electrons. They are arranged in a column on the Periodic Table *(top)* to reflect this shared feature. Fluorine, chlorine, bromine and iodine are found naturally. Many organohalogen compounds are synthesized inside living organisms and by industrial chemists. A partial list of compounds mentioned in this article appears at left.

global production of methyl bromide by rapeseed plants alone is about 6,600 tons per year—or 15 percent of the total from human activities.

Evergreen trees and potato tubers, among other familiar plant species, produce methyl chloride. The widespread synthesis of this chemical makes it the most abundant chlorinated compound—of any source—in the atmosphere. Other notable organochlorines include growth hormones in beans and peas, a cocktail of seven fungicides produced by the edible Japanese lily, and 2,4-dichlorophenol, produced by a *Penicillium* mold as a growth hormone. This last chemical is widely employed to manufacture several other compounds, including the herbicide "2,4-D," which was one-half of the Vietnam War–era defoliant Agent Orange.

A few fluorocarbons also exist in nature, although they are rare because of the low bioavailability of fluorine. The most notorious is fluoroacetic acid, which is found in several plants indigenous to Australia and southern Africa. This compound is extremely poisonous and has killed thousands of livestock unlucky enough to eat it. In fact, fluoroacetic acid was once widely used as a pesticide, "1080," by farmers in the western United States to kill coyotes and rodents. The toxicity of 1080 comes from its interference with the Krebs biochemical cycle, thereby causing a fatal buildup of citric acid.

Halocarbons in Higher Animals

Arthropods and vertebrates also synthesize an array of organohalogens, although not with the same profligacy as marine plants and animals. The compound 2,6-dichlorophenol is made by females of more than a dozen tick species as a sex pheromone. The German cockroach synthesizes two other chlorinated pheromones to induce aggregation. And chloroform, which was used as an anesthetic during the mid-19th century and is now a common industrial solvent, has a number of natural sources. Chief among them are termites, which emit 15 percent of global atmospheric chloroform, perhaps as a waste product of the chloride compounds naturally present in wood.

The tiny poison-arrow frog *Epipedobates tricolor* is a native of Ecuador that secretes epibatidine, a chlorine-containing substance with a chemical structure unique to science. Epibatidine is 500 times more potent than morphine

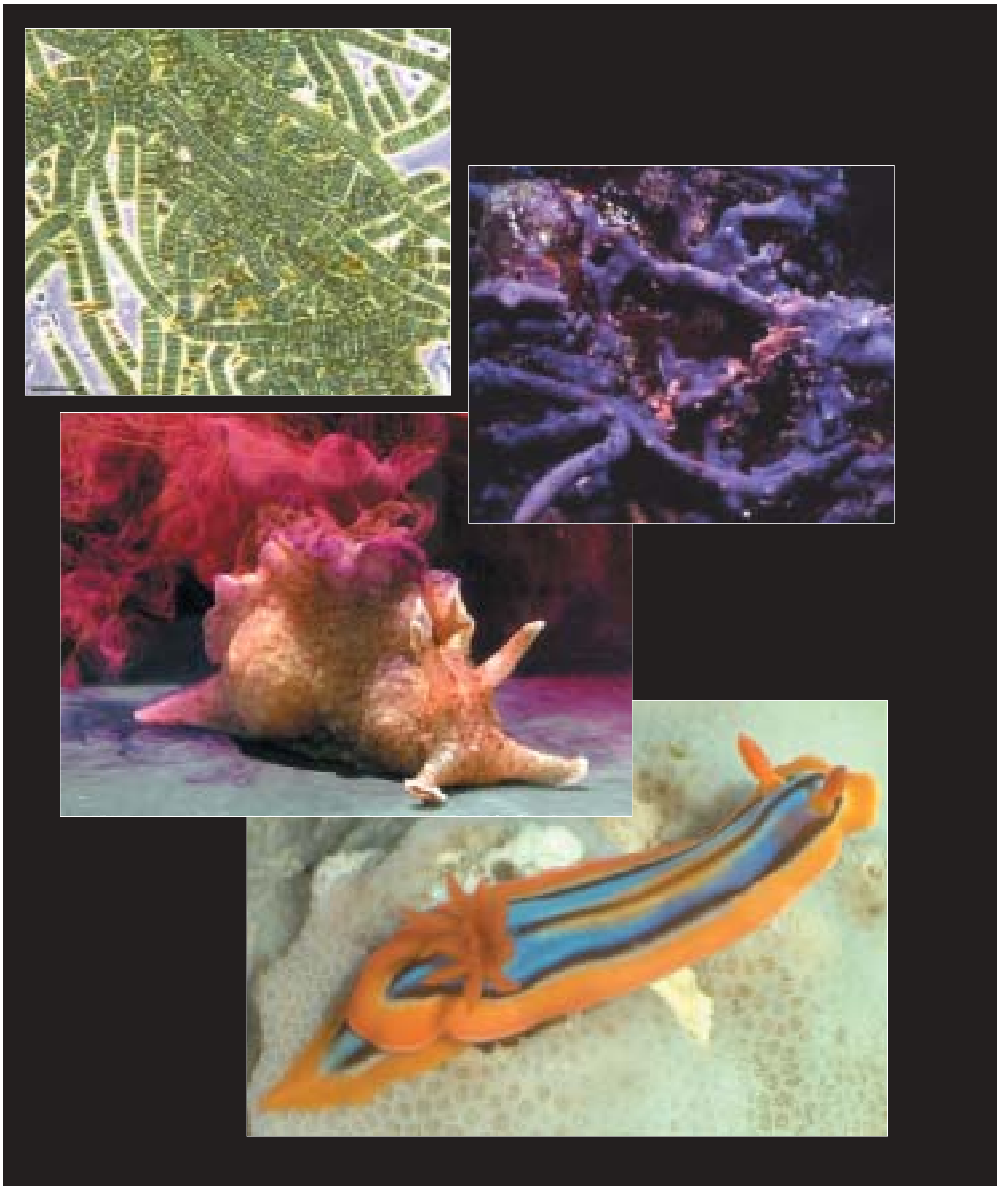


Figure 3. Marine species are the richest sources for organohalogens. The filamentous blue-green algae *Lyngbya (top left)* synthesizes aplysiatoxin, the cause of "swimmer's itch." The sponge *Dysidea dendyi* produces several brominated dioxins; its close kin *Dysidea granulosa* is shown here *(top right)*. *Aplysia californica (middle)* is a sea hare that emits ink derived from its algal diet—the same source for halogenated defensive compounds used by many other species of sea slugs. The brilliantly colored nudibranch *Chromodoris hamiltoni (bottom)* also creates its own chlorinated metabolites. (Photographs courtesy of Rolf Schauder, Mark Schneegurt and www-cyanosite.bio.purdue.edu *(Lyngbya)*, Francis Schmitz *(Dysidea)*, Genevieve Anderson *(Aplysia)* and Bill Rudman and www.seaslugforum.net *(Chromodoris)*.)

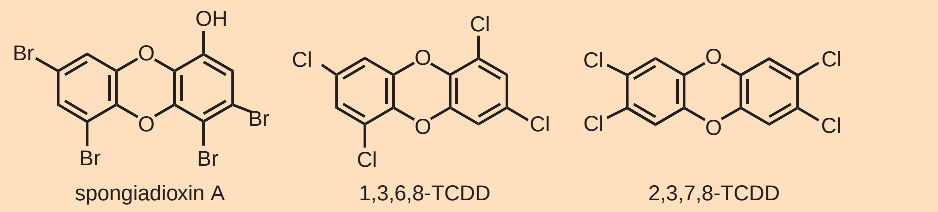


Figure 4. Dioxins are toxic compounds, but not all are made by human chemists. These three have very different sources: From left, spongiadioxin A from *Dysidea dendyi*; 1,3,6,8-tetrachlorodibenzo-p-dioxin (1,3,6,8-TCDD), a natural dioxin formed during the decay of plant matter in New Brunswick peat bogs; and 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), an industrial chemical.

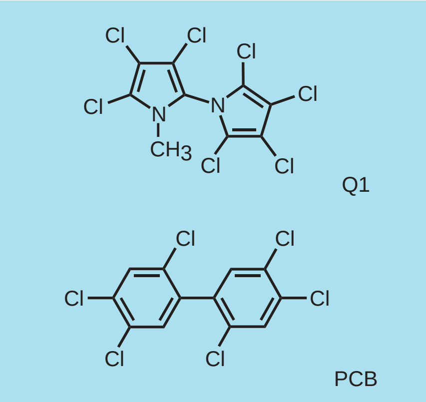
as a painkiller, which has led the pharmaceutical industry to explore synthetic analogues as novel analgesics. The chemical's original purpose may have been to thwart potential predators.

Our own species naturally produces the iodinated hormone thyroxine, which regulates basal metabolism and was thought for a hundred years to be the only organohalogen made by the human body. However, recent studies demonstrate that our bodies produce bleach (hypochlorous acid) and chlorine gas! White blood cells use chloride and the enzyme myeloperoxidase to kill microbial pathogens and perhaps tumor cells. Byproducts of these reactions include chlorinated proteins and nucleic acids. This chlorination process is an essential component of the immune system: Humans deficient in myeloperoxidase are highly susceptible to bacterial infections, particularly pneumonias. Of the few organobromines synthesized by human cells, the first to be found, a bromoester in cerebrospinal fluid, induces REM (rapid-eye-movement) sleep.

Rock and Fire

Although living things overwhelmingly utilize organochlorines and organobromines in preference to other halocarbons, fluorine is actually the most abundant halogen in the Earth's crust: Volcanoes emit 11 million tons of hydrogen fluoride and 3 million tons of hydrogen chloride per year. Given this abundance, it comes as no surprise that at the high temperatures and pressures deep within the Earth, organic matter such as peat combines with chloride and fluoride minerals to form carbon-containing halogenated chemicals. Volcanoes on at least four continents (Asia, Europe, North and South America) emit these naturally formed organochlorine and organofluorine gases. Some of the resulting compounds are identical to some of the anthropogenic CFCs that catalyze the breakdown of stratospheric ozone.

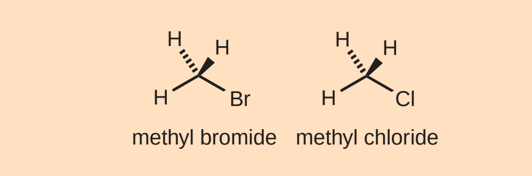
Rock also contains organohalogens, which can exist as pockets of gas or a component of certain minerals. When some rocks are crushed during mining, methyl chloride, dichloromethane, chloroform, carbon tetrachloride and other chlorinated chemicals are released. Potassium-salt mining alone liberates thousands of tons of chloroform per year, and several natural fluorite minerals contain tetrafluoroethylene—



Q1

PCB

Figure 5. Many top-level marine consumers, including bottlenose dolphins *(Tursiops truncates, left)* penguins, seals and humans, show bioaccumulation of the natural organochlorine compound Q1 *(top structure)*. Q1 is sequestered in fatty tissues in a manner similar to industrial PCBs, or polychlorinated biphenyls *(bottom structure)*. (Photograph courtesy of the National Oceanic and Atmospheric Administration.)



methyl bromide methyl chloride

Figure 6. Two natural methyl halide sources: In the foreground, rapeseed plants, the source of canola oil, emit about 15 percent of anthropogenic methyl bromide. The evergreen trees in the background are significant sources of methyl chloride. (Photograph courtesy of the Canola Council of Canada.)

Patrick Robert/Corbis Sygma

Figure 7. Volcanic gases, such as those from the Pu'u 'O'o cone of Kilauea volcano on the island of Hawaii *(left)*, can contain many organohalogen compounds, including CFC-11, once used as a refrigerant before it became linked to the destruction of stratospheric ozone. Forest and grassland fires *(right)*, most of which are set by humans, give off large quantities of methyl chloride and methyl bromide, which also catalyze ozone breakdown. (Photograph at left courtesy of Richard Hoblitt, Hawaiian Volcano Observatory, U.S. Geological Survey.)

the chemical precursor to Teflon. One dark purple fluorite from Bavaria exudes the unmistakable smell of fluorine gas when crushed, earning it the name "stinkspat" among local miners. Halogens aren't confined to terrestrial chemistry: Hydrogen chloride and hydrogen fluoride are also present in interstellar space, and at least four meteorites have contained chlorinated compounds.

Significant amounts of nonbiogenic organohalogens come from burning biomass. People set most fires; only 10 percent are caused by lightning or other natural sources. Together, these sources of biomass combustion release large quantities of methyl chloride (900,000 tons per year) and lesser amounts of methyl bromide (10,000 to 50,000 tons per year). The global input per year of atmospheric methyl chloride is estimated at 4 million tons. These figures dwarf the 10,000 tons per year coming from industry.

Chemistry of Creation and Destruction

How does nature produce these compounds? Many recent studies have asked this question, leading to widespread recognition of biogenic halogen cycles. Halide salts are present in massive quantities for chemical conversion to halogen. The world's oceans contain 27 quadrillion tons of chloride and 89 trillion tons of bromide, and the Earth's crust contains 45 quadrillion tons of chloride and 190 trillion tons of bromide.

Bromoperoxidase (BPO) and chloroperoxidase (CPO) are common enzymes that play important roles in the cycles of their respective halogens. In combination with hydrogen peroxide, they oxidize bromide and chloride to hypobromite and hypochlorite (which in aqueous solution forms hypochlorous acid, or household bleach). Of 94 species of red algae, 71 show bromoperoxidase activity; several marine diatoms also contain BPO. Another

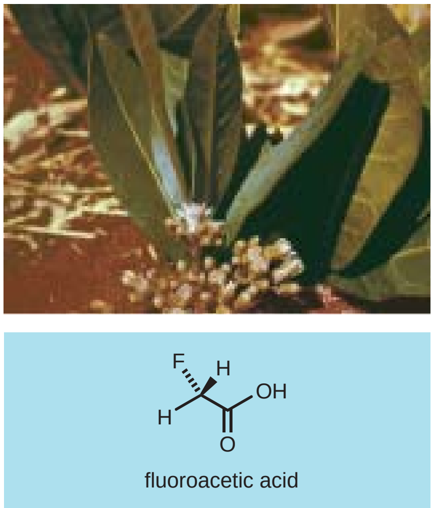


Figure 8. *Dichapetalum cymnosum* or gifblaar, a native South African plant, is one of several species in Africa and Australia that produce fluoroacetic acid. This chemical interferes with the Krebs cycle, a property dangerous to livestock that eat the plant but valuable when packaged as the commercial pesticide "1080." (Photograph courtesy of the Bristol Biomedical Image Archive.)

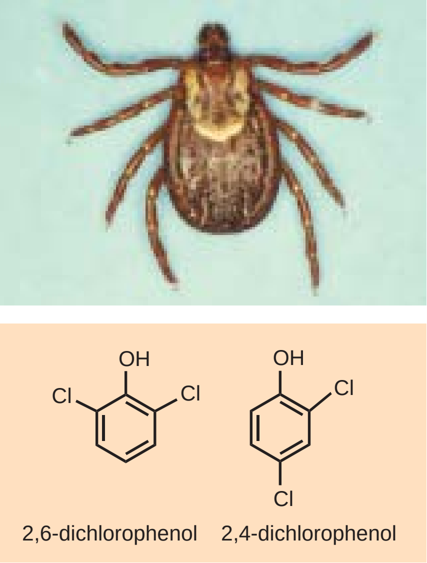


Figure 9. Females of 14 tick species, including the American dog tick *Dermacentor variabilis,* use the chemical 2,6-dichlorophenol *(left)* as a pheromone. The isomer 2,4-dichlorophenol *(right)* is a broad-spectrum herbicide that made up one-half of the Vietnam War–era defoliant Agent Orange. (Photograph courtesy of University of Nebraska Department of Entomology.)

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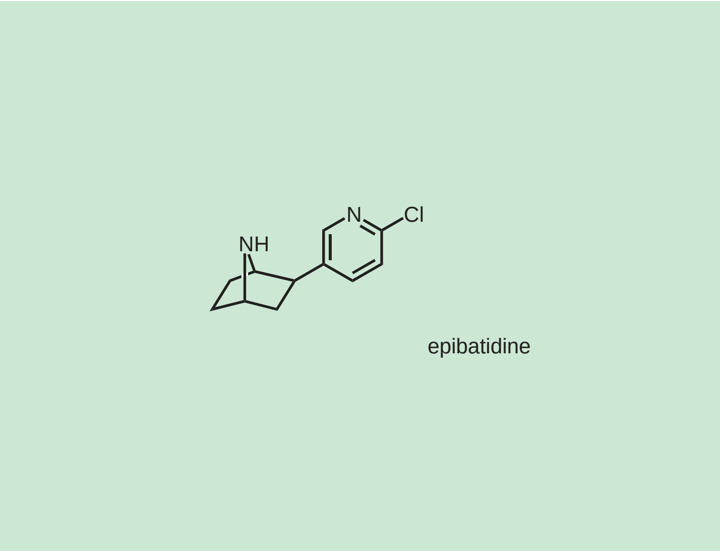

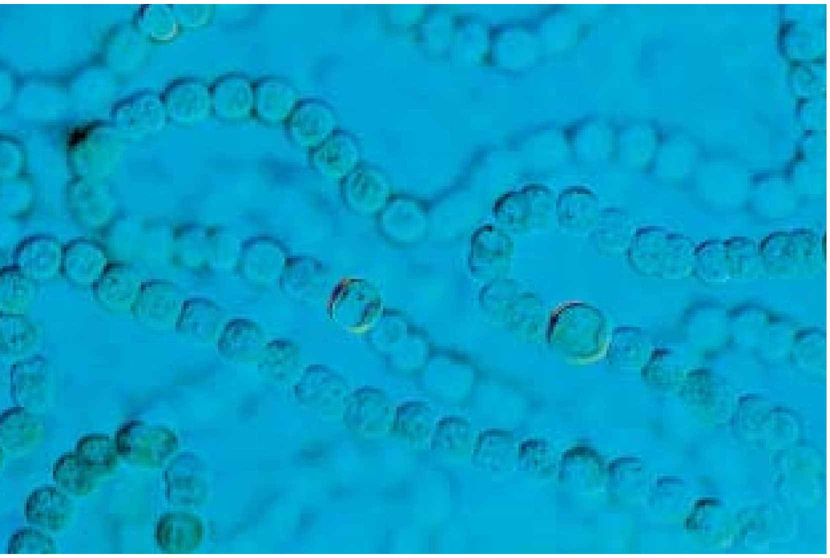

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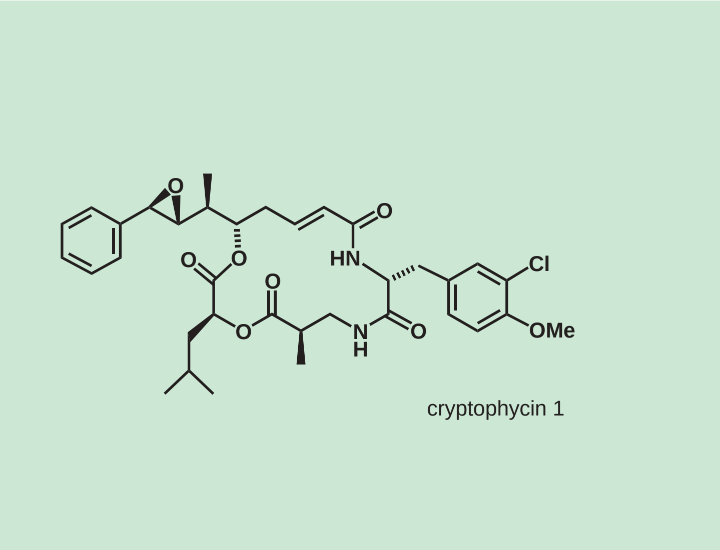

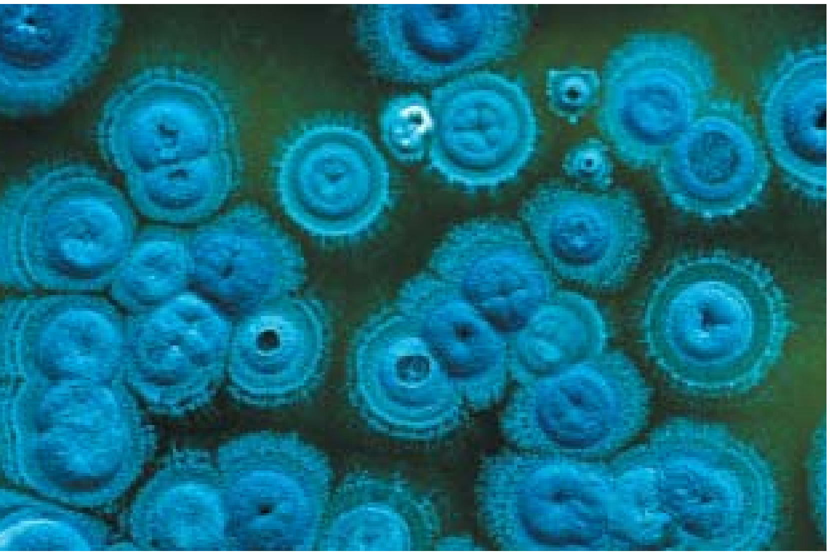

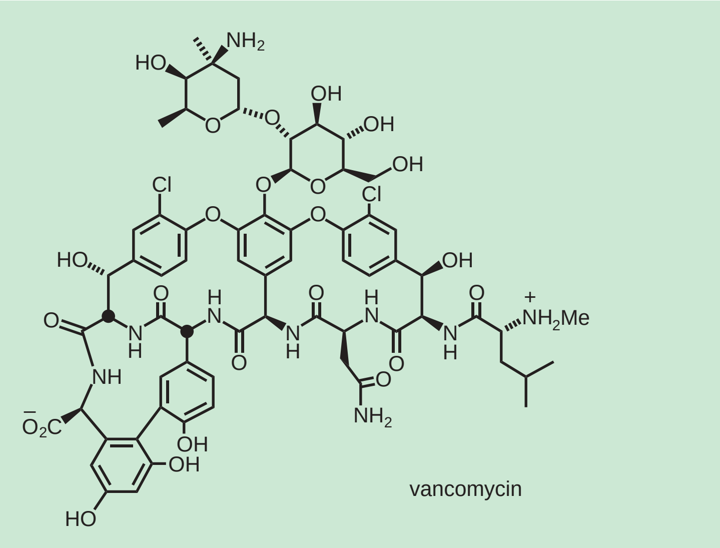

Figure 10. Several important drugs are organohalogens from natural sources. The poison-arrow frog *Epipedobates tricolor* secretes epibatidine, a painkiller 500 times more potent than morphine *(top)*. The blue-green algae *Nostoc* produces the anti-cancer drug cryptophycin *(middle)*. And the antibiotic vancomycin is derived from *Streptomyces orientalis* (now called *Amycolatopsis orientalis*), a relative of *Streptomyces coelicolor* *(bottom)*. The complexity of chemical metabolites has little relation to the species of origin. (*S. coelicolor* photograph courtesy of Tobias Kieser, John Innes Centre, U.K.)

source of free chlorine is the oxidation of saltwater spray by ozone over the ocean's surface. Subsequent reactions with organic compounds can produce organochlorines.

Biochlorination is part of an important pathway in the recycling of organic plant matter. Each year, an estimated 63 billion tons of plant material degrades into humic acid, which is acted on by CPO in the presence of sodium chloride to afford chlorinated humic acid. This complex polymeric substance undergoes extensive degradation first to chlorophenols and then to chloroacetic acids and chloroform. Chlorophenols can also undergo dimerization to form dioxins in an amazing natural process that occurs in the soil of New Brunswick peat bogs and Douglas fir forests in Sweden, as well as more prosaic settings such as fresh compost, sewage sludge and cow feces.

Chemists have duplicated this sequence of chemical reactions in the laboratory. They have also isolated chlorinated humic acids from 5,200-year-old groundwater reservoirs and 35,000-year-old organic matter. Organochlorines have also been identified in lignite samples from 15 million years ago during the Tertiary period, and in a 300-million-year-old coal sample. Cyano-bacteria (blue-green algae), which synthesize many organochlorines, have existed for billions of years. Thus, organohalogens have been with us since the beginning of life on Earth, and they certainly predate the arrival of humans.

Tip of the Therapeutic Iceberg?

People have collected and used organohalogen compounds for millennia. The dye Tyrian purple, a bromine-containing analogue of blue indigo, was extracted from the Mediterranean mollusk *Murex.* References to its production in the Phoenician (Greek for "land of the purple") city of Tyre appear in texts from about 1600 B. C. This rare, brilliantly colored dye became an early staple of the Phoenician trading empire and was adopted as a symbol of royalty among the Romans, Egyptians and Persians. Today we have a different, but equally precious, use for unique halocarbons.

Many naturally occurring organohalogens exhibit biological activity that may offer unprecedented benefits to humankind. Vancomycin is a lifesaving antibiotic that is often the last line of defense against multi-drug-resistant bacteria. With respect to mosquito larvae, the chlorinated seaweed metabolite telfairine is as potent an insecticide as the compound lindane (benzene hexachloride), which consumer advocates have criticized because of its suspected toxicity to humans. A chlorinated fungal metabolite called maracen is active against mycobacteria, the cause of tuberculosis, and the chlorine-containing punaglandins, from a South Pacific soft coral, have potent antitumor activity and may soon find clinical use.

Another promising anticancer agent is cryptophycin, an organochlorine compound that is derived from the blue-green algae *Nostoc* and is more efficacious than the commercial anticancer drugs Taxol or vinblastine in early tests. Clinical trials for at least one synthetic analogue are under way. In this molecule, the presence of chlorine is critical—removal of the halogen atom cuts the activity of the drug by an order of magnitude. Spongistatin 9, a chlorine-containing sponge metabolite, is one of the most potent compounds ever tested among 60 tumor-cell lines at the National Cancer Institute. Other new organohalogens inhibit viruses, including HIV.

In their search for novel medicines, natural-products chemists discover 100 to 200 new organohalogens each year, mostly from marine sources. Given that only a small percentage of the estimated 500,000 species of marine animals, plants and bacteria have been chemically evaluated, thousands of novel, natural organohalogens await discovery. In the case of primitive bryozoans, most of the several dozen species that have been analyzed produced distinct organohalogens. Approximately 3,900 species have not yet been tested.

As Natural as Anything

Halogens are as natural to our ecosystem as carbon, hydrogen, oxygen, nitrogen and the other elements of life. Biogenic organohalogens are similar to the multitude of other chemicals that constitute living things: They play essential roles for the survival of the organism. Along with other biomolecules, halogenated hormones and defensive chemicals have evolved under the stress of natural selection to serve specific functions.

Yet the long, and growing, list of natural organohalogens does not imply that their synthetic analogues are always benign, as if "natural" somehow equaled "harmless." On the contrary, halogen-containing compounds are often biologically active, as many of the examples in this article have shown. Negative environmental consequences of halocarbons such as CFCs, halons, chlorinated solvents, DDT, PCBs and dioxins are well known.

The discovery that some anthropogenic halocarbons are also made naturally requires a broader assessment of environmental risk—one that does not depend on the origin of the chemical. It is axiomatic that when the sum of natural and anthropogenic sources becomes an unacceptable risk, then the human contribution must be reduced. For this determination to be made, scientists must know the proportions that come from industry *and* nature—a task that demands greater understanding of the biogeological sources and sinks of these chemicals.

Acknowledgments

This article is dedicated to the memory of Professor Walter Stockmayer, a world-renowned polymer chemist, member of the National Academy of Sciences and dear colleague. He recently passed away at age 90.

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