Natural Chlorine Updates – No. 2

November 15, 1995

Dr. Gordon W. Gribble
Department of Chemistry
Dartmouth College
Hanover, New Hampshire 03755 USA
FAX: 603-646-3946
Phone: 603-646-3118
e-mail: grib@Dartmouth.edu

I. Introduction

This literature review is the second in a series of periodic updates to the natural halogen literature, with a particular focus on organochlorine compounds.

The coverage is approximately from mid-June 1995 to mid-November 1995, with inclusions of earlier material as appropriate.

Several important events have occurred in recent months in the chlorine arena. The American Chemical Society national meeting in Chicago, August 20-24, 1995, sponsored a Symposium on "Chlorine and Chlorine Compounds in the Paper Industry". This four-day symposium, which was organized by Dr. Victor Turoski (*1*) featured forty papers by speakers from industry, academia, and regulatory agencies. The Symposium concluded with a Risk Assessment Panel. Additional details about this important event are presented in Section VI.

A brochure entitled "Chlorine and Health" has just been published by the American Council on Science and Health (*2*). This peer-reviewed document discusses the role of chlorine in our society and its benefits to human health. For example, it examines chlorine in the paper industry, water purification using chlorine, polyvinylchloride, and some of the current controversies involving dioxin and the alleged estrogenic effects of chlorinated chemicals.

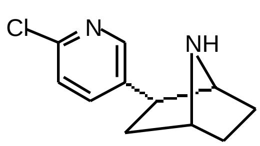
An account of the seminar "Chlorine and Life" has recently been published by the Environmental Center of Polytechnic University of Catalunya (*3*). This special October 1994 seminar, which featured speakers from around the world, both industrial and academic, was attended by more than 300 participants. Details about this conference are presented in Section V.

The monograph "Naturally Occurring Organohalogen Compounds — A Comprehensive Survey", which documents nearly 2500 organohalogen compounds and contains 2300 references, will be published early in 1996 as Vol. 68 of *Progress in the Chemistry of Organic Natural Products* by Springer-Verlag. A recent review of natural chlorine has appeared in *Chemistry in Britain* (*4*), and the Euro Chlor publication "The Natural Chemistry of Chlorine in the Environment" has been widely distributed to interested parties by this author.

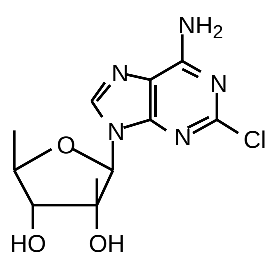
II. New Natural Organohalogens

The discovery of novel naturally occurring organohalogen compounds continues at an unabated pace, particularly from marine sources (*5*). Fifty-five new natural organohalogen compounds are reported herein, bringing the total of known compounds to 2530. Facilitated by new, more powerful Nuclear Magnetic Resonance (NMR) spectroscopic characterization techniques, natural products chemists can identify literally miniscule amounts of compounds. Moreover, the development of new enzyme-based screening protocols has greatly improved the discovery of biologically active organohalogen natural products.

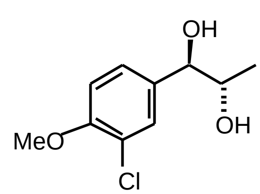
The extraordinarily interesting Ecuadoran poison frog metabolite epibatidine (**1**), which is 500-1000 times more potent than morphine as an analgesic, has been featured in a *Fortune* magazine article (*6*). The previously known sponge metabolites bastadin 5 and 19, which are produced by *Ianthella basta*, are now commercially available (Calbiochem, LaJolla, California) as tools to study ryanodine binding and calcium transport (*7*, *8*). Methyl chloride has been detected in the air above a spruce forest (*9*). The novel chlorinated nucleoside kumusine (**2**) has been isolated from the sponge *Theonella* sp. (*10*) and, independently, as trachycladine A from the sponge *Trachycladus laevispirulifer* (*11*). The fungus *Trametes* sp. has yielded the novel trametol (**3**) (*12*), and the trichloromethyl metabolite herbamide A (**4**) has been found in the sponge *Dysidea herbacea* from Papua, New Guinea (*13*). The terrestrial plant *Vellozia bicolor* from Brazil contains diterpene **5** (*14*). Interestingly, the corresponding epoxide is not converted to **5** under the isolation conditions.



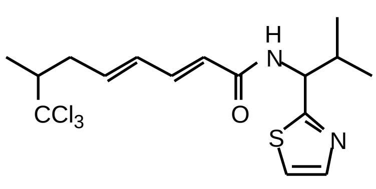
1 (epibatidine)



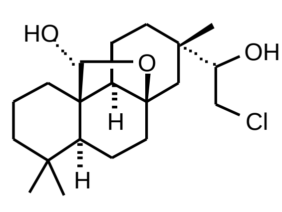
2 (kumusine)



3 (trametol)

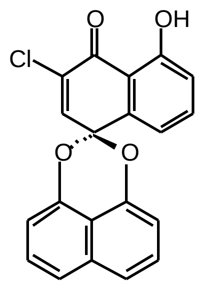


4 (herbamide A)

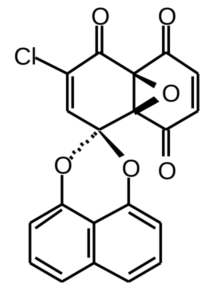


5

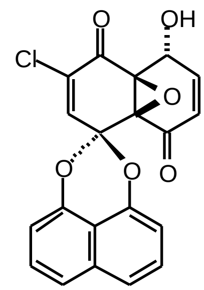
The four novel antibacterial, antifungal, and herbicidal palmarumycins **6**-**9** have been discovered in the West Borneo forest soil microbe *Coniothyrium* sp. along with several other related nonchlorinated metabolites (*15*). The toxic mushroom *Russula subnigricans* produces the optically active chlorohydroquinone tetramer russuphelol (**10**) (*16*), in addition to chlorinated hydroquinones russuphelins A-F (**11-16**) (*17*, *18*).



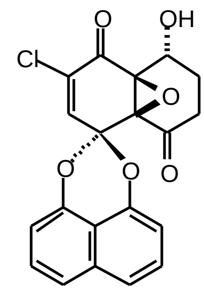
6 (palmarumycin C_1)



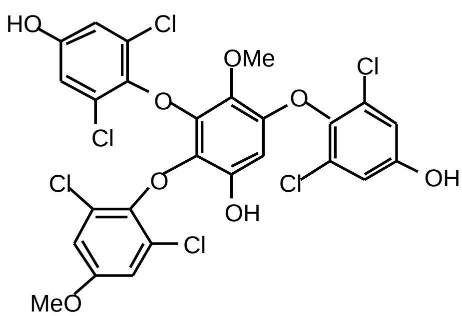
7 (palmarumycin C_4)



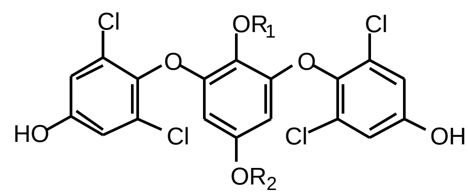
8 (palmarumycin C_7)



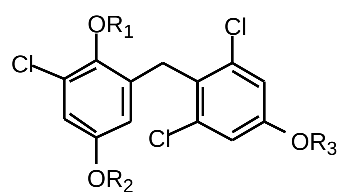
9 (palmarumycin C_8)



10 (russuphelol)

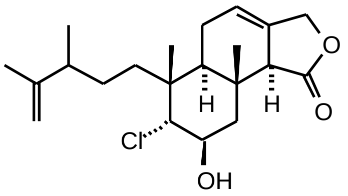


11 $R_1 = R_2 = Me$ (russuphelin A)
12 $R_1 = Me, R_2 = H$ (russuphelin B)
13 $R_1 = R_2 = H$ (russuphelin C)

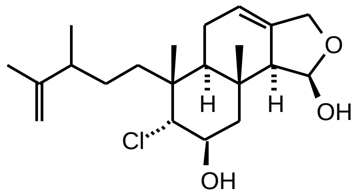


14 $R_1 = R_2 = Me, R_3 = H$ (russuphelin D)
15 $R_1 = R_3 = Me, R_2 = H$ (russuphelin E)
16 $R_1 = H, R_2 = R_3 = Me$ (russuphelin F)

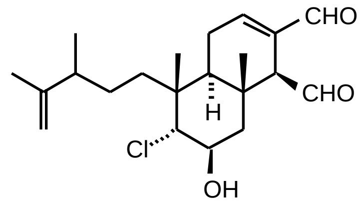
The unusual chlorinated homo-diterpenes hamiltonins A-D (**17-20**) are secreted by the South African nudibranch *Chromodoris hamiltoni* (*19*), and the freshwater blue-green alga *Microcystis aeruginosa* produces the trypsin inhibitor aeruginosin 98-A (**21**) (*20*). The three potent novel chitinase inhibitors, styloguanidines **22-24** have been isolated from the sponge *Stylotella aurantium* in the Yap sea (*21*). The terrestrial plant *Jaborosa sativa* has afforded the chlorosteroid jaborosalactone T (**25**) (*22*).



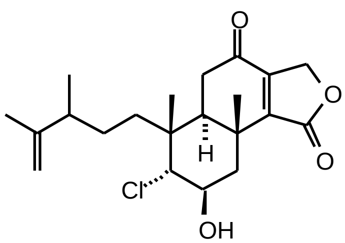
17 (hamiltonin A)



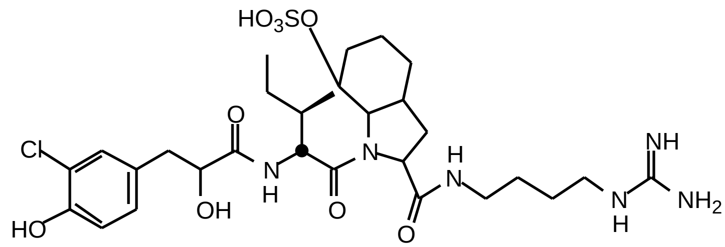
18 (hamiltonin B)



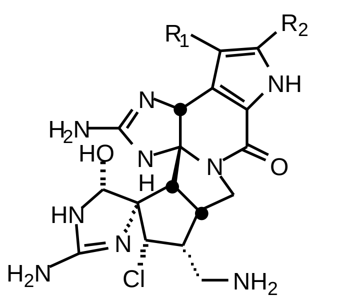
19 (hamiltonin C)



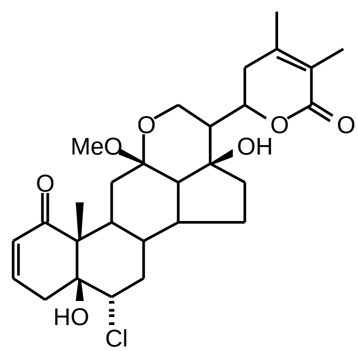
20 (hamiltonin D)



21 (aeruginosin 98-A)

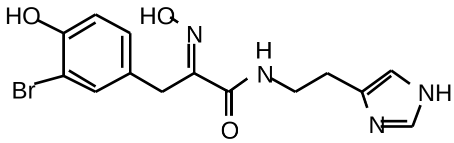


22 $R_1 = R_2 = H$ (styloguanidine)
23 $R_1 = Br, R_2 = H$
24 $R_1 = R_2 = Br$

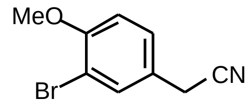


25 (jaborosalactone T)

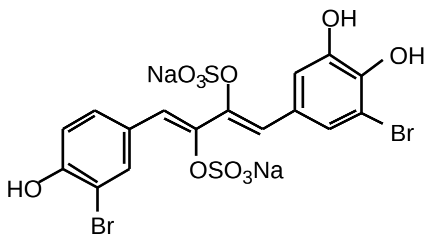
Not surprisingly, a number of new organobromine compounds have also been isolated from natural sources in the past six months. Thus, the Caribbean sponge *Pseudoceratina crassa* produces the new bromo compounds **26** and **27** (*23*), and the deep water Grand Bahama Island sponge *Aplysina fistularis fulva* has afforded aplysillin A (**28**), a novel disulfate (*24*). The sponge *Psammaplysilla purpurea* has yielded the new dibromoanisic acid **29** in addition to **27** (*25*), and the New Zealand sponge *Hamigera taragensis* has afforded the novel bromo lactone **30** (*26*). The Japanese sea hare *Aplysia parvula* secretes aplyparvunin (**31**), which displays ichthyotoxicity (*27*).



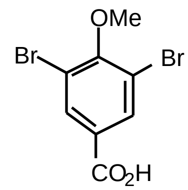
26



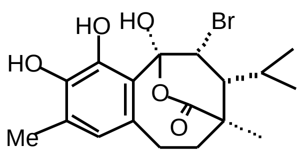
27



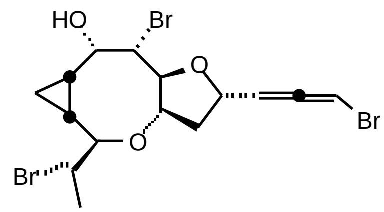
28 (asplysillin A)



29

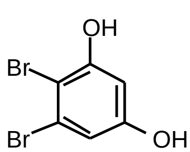


30

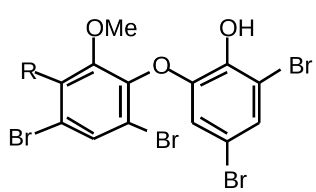


31 (aplyparvunin)

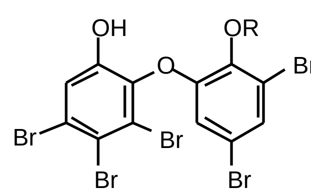
A large number of halogenated metabolites have been isolated from *Dysidea* sp. sponges and a recent study reported the presence of six new organobromine compounds **32**-**37** in this animal (*28*). These metabolites exhibit inhibition of inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, and 15-lipoxygenase. The Pohnpei sponge *Dysidea fragilis* has been found to contain the novel antazirines **38** and **39** (*29*). The New Caledonian sponge *Orina* sp. produces the four novel bromoindoles **40**-**43** in addition to the previously known gelliusines A and B (*30*).



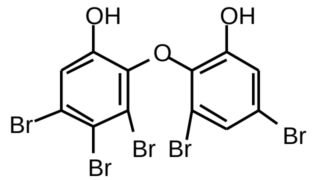
32



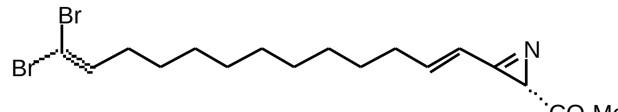
33 R = H
34 R = Br



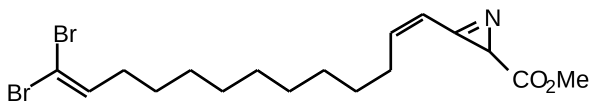
35 R = H
36 R = Me



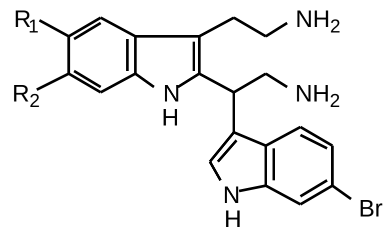
37



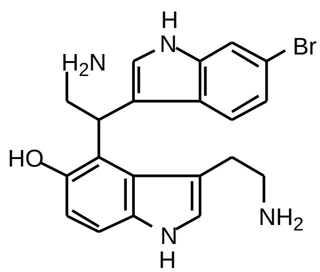
38 ((4*E*)-*S*-antazirine)



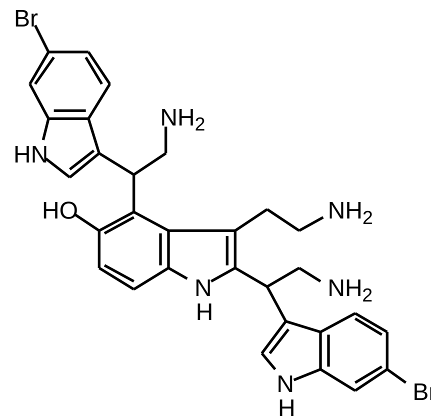
39 ((4*Z*)-antazirine)



40 R_1 = OH, R_2 = H
41 R_1 = H, R_2 = Br

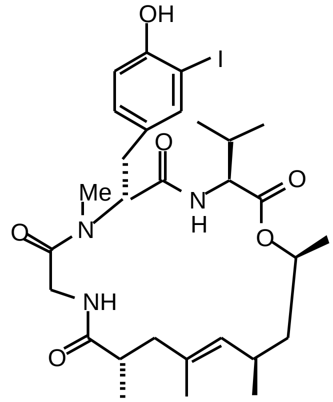


42

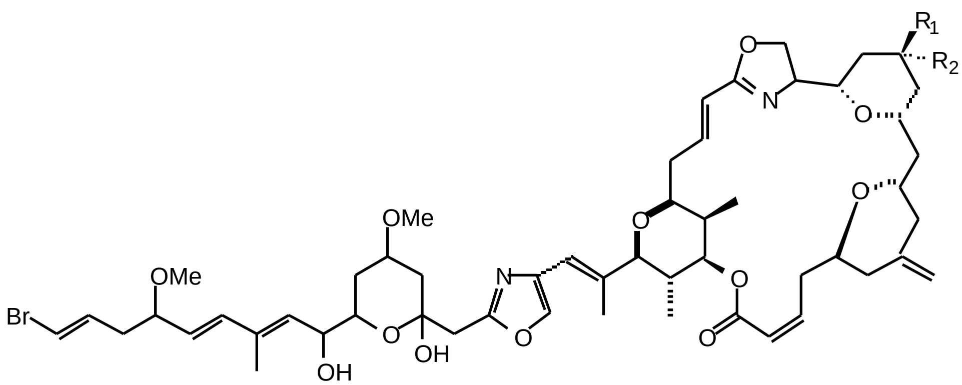


43

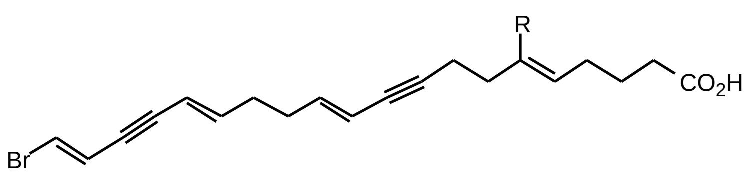
Sponges also produce halogenated cyclic peptides (depsipeptides) and the Japanese sponge *Halichondria cylindrata* has yielded halicylindramides A-C (not drawn), each of which contains the 4-bromo-L-phenylalanine amino acid (*31*). The sponge *Neosiphonia superstes* produces the iodo neosiphoniamolide A (**44**) (*32*), which is very similar to geodiamolide TA as described in *Chlorine Updates #1*. The Western Australian sponge *Phorbas* sp. contains the very potent cytostatic macrolides phorboxazoles A (**45**) and B (**46**) (*33*). The three new brominated fatty acids **47-49** are found in the Indian Ocean sponge *Xestospongia* sp. (*34*). Two other new brominated fatty acids, **50** and **51**, are found in the sponge *Amphimedon terpenensis* along with a previously known compound (n = 14) (*35*). Another study found **52** and **53** in the sea anemone *Stoichactis helianthus* (*36*).



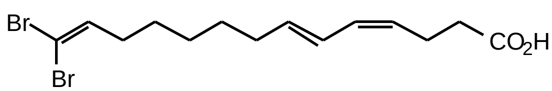
44 (neosiphoniamolide A)



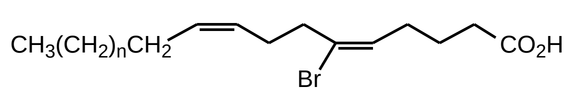
45 R_1 = OH, R_2 = H (phorboxazole A)
46 R_1 = H, R_2 = OH (phorboxazole B)



47 R = H
48 R = Br



49



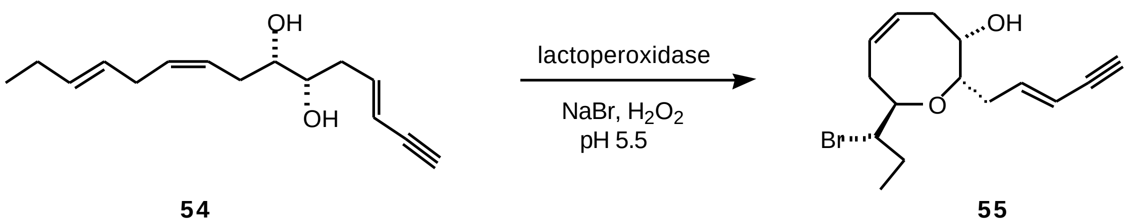
50 n = 12
51 n = 13
52 n = 9
53 n = 10

III. Biohalogenation

The mechanisms whereby organisms biosynthesize halogen-containing compounds remain of keen interest and a special symposium on "Biohalogenation" was held in September, 1995, at

Purdue University (*37*). This one-day symposium featured lectures by Drs. H. B. Dunford (Alberta), A. Butler (Santa Barbara), L. P. Hager (Illinois), R. Wever (Amsterdam), K.-H. van Pée (Stuttgart), and M. Sundaramoorthy (Irvine). Chloroperoxidases, bromoperoxidases, and other haloperoxidases were discussed. For example, Dunford has recently investigated the mechanisms of the chlorination of taurine by myeloperoxidase (*38*) and the iodination of tyrosine by peroxidase (*39*). Hager has studied the chemistry of chloroperoxidase with terminal alkenes and alkynes (*40*).

The biosynthesis of the brominated tyrosines in the sponge *Aplysina fistularis* has been reported in detail (*41*). The biosynthesis of various *Laurencia* red algae metabolites from laurediols and lactoperoxidase/NaBr/H_2O_2 has been examined experimentally and using molecular modeling (*42*). For example, (3*E*, 6*S*, 7*S*)-laurediol (**54**) cyclizes to (*E*)-prelaureatin (**55**) as shown. Results such as these support the bromonium ion pathways that have been proposed for the formation of the numerous *Laurencia* cyclic bromo ethers.



The production of several volatile organohalogens by the red alga *Meristiella gelidium* has been studied in batch culture (*43*). The formation of $CHBr_3$, $CHBr_2Cl$, $CHBrCl_2$, $CHCl_3$, $HClC{=}CCl_2$, CH_2Br_2, CH_2I_2, CH_2ClI, *n*-C_4H_9I, and CH_3I requires both hydrogen peroxide and peroxidase. For example, the production of $CHBr_3$, $CHBr_2Cl$, CH_2Br_2, and CH_2ClI in several unialgal cultures of marine phytoplankton has been demonstrated (*44*).

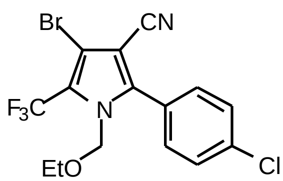
IV. Function and Biological Studies

The naturally occurring chlorophenolic glycopeptide antibiotics such as vancomycin have assumed a crucial role in the treatment of penicillin-resistant bacterial infections (*45*), such as that induced by *Staphylococcus aureus*, the frequently lethal "super germ" (*46*). Yearly sales of vancomycin and the related teicoplanin, which also contains the chlorophenol unit, are in the hundreds of millions of dollars. Detailed NMR studies have been reported of the structure formed between the glycopeptide ristocetin A and a bacterial cell wall analog (*47*).

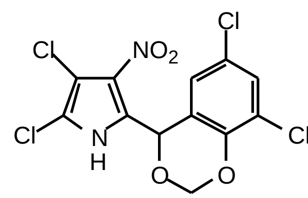
Studies of the chlorophenolic antitumor antibiotic C-1027 have revealed the importance of the benzoxazoline ring in DNA intercalation (*48*).

The role of volatile marine organohalogens such as CH_2ClI and CH_3I may be to transport iodine from ocean to atmosphere, and recent evidence indicates that CH_2ClI may be comparable to CH_3I in iodine transport (*49*).

The new halogen-containing pesticide "Pirate" (**56**) (American Cyanamid) was discovered by chemically modifying the naturally occurring dioxapyrrolomycin (**57**).



56 ("Pirate")



57 (dioxapyrrolomycin)

V. "Chlorine and Life" Symposium

This special symposium on chlorine was held at the Polytechnic University of Catalunya in Barcelona in October 1994 and was organized by the Environmental Center of the University (*3*). In addition to several talks of a general nature, this seminar featured presentations by Dr. Ed de Leer on "The Natural Chlorine Cycle," Dr. James Franklin on "The Atmospheric Degradation and Impact of Chlorinated Aliphatic Hydrocarbons," and Dr. Christoffer Rappe on "Sources, Environmental Levels and Historical Trends of Chlorinated Dioxins."

Professor de Leer reiterated the importance of the natural chlorine cycle and summarized the enormous quantities of CH_3Cl, $CHCl_3$, and $CHBr_3$ that are produced in the arctic ocean. It is speculated that the seasonal production of these compounds may be linked to similar variations in the ozone hole over the arctic. There is a growing proposal that the marine boundary layer is another source of natural organohalogens. Thus, sea salt spray may be oxidized to active chlorine by ozone or nitrogen oxides, followed by reaction with natural hydrocarbons to give organohalogens. A very exciting discovery is the confirmation that $CHCl_3$ is produced in humic top soils by means of a ^{37}Cl "feeding" experiment. This supports the notion that chloride can be oxidized to active chlorine with soil chloroperoxidase which reacts with humic acid substances leading ultimately to chloroform.

In his presentation Dr. Franklin discussed the impact of halogenated chlorofluorocarbons (CFCs), partially halogenated hydrochlorofluorocarbons (HCFCs), and simple chlorinated solvents (CH_2Cl_2, $Cl_2C{=}CHCl$, $Cl_2C{=}CCl_2$) on the environment and, in particular, on the ozone layer. Most significantly, the latter three solvents have only an insignificant impact on stratospheric ozone depletion, tropospheric ozone formation, global warming, or acid rain.

Dr. Rappe reiterated the fact — supported by new studies of ancient sediments — that dioxins have natural sources. He pointed out that, due to the obvious sampling problems, only one study has confirmed the prediction that dioxins and the related polychlorodibenzofurans can be formed in forest fires (*50*). Furthermore, other studies have shown that dioxins can form photochemically from (natural) chlorophenols (*51*), and enzymatically from sewage sludge (*52*) and fresh garden compost (*53*). Although significantly lower than post-industrial levels of dioxins, abiotic samples of ancient deposits reveal surprisingly high levels of dioxins. For example, dioxins have been identified in 8000 year-old deep sediments in Japan (*54*), and Baltic Sea sediments dating back to 1880 contain dioxins and furans as reported by Dr. Rappe in his presentation. See also reference *53*. Also, archived UK soil and herbage samples, 100-150 years old, have concentrations of dioxins and furans about one-third of the levels found today (*53*).

VI. "Chlorine and Chlorine Compounds in the Paper Industry" — Chicago, August 1995

The Chicago 1995 American Chemical Society Symposium "Chlorine and Chlorine Compounds in the Paper Industry," which was sponsored by the Division of Environmental Chemistry, was divided amongst the following sessions.

1. Current and Proposed Bleaching Alternatives
2. Analytical and Environmental Aspects
3. Public Perceptions
4. Regulatory Aspects
5. Toxicology and Mechanisms

6. Risk Assessment Panel Discussion

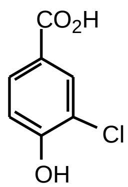
The American Chemical Society will publish a peer-reviewed book based on this Symposium (*55*).

While most of the papers presented at this symposium dealt with chlorine in the paper industry and the formation of anthropogenic organochlorines, a few papers discussed the possible role of natural organochlorine compounds in the paper industry. Dr. Anders Grimvall emphasized that the large scale production of organohalogens, particularly organochlorines, occurs in terrestrial environments by the enzymatic chlorination of humic acid substances and their subsequent conversion to chloroform, chlorophenols, and chloroacetic acids. This work is discussed further in the next section. Dr. Grimvall also noted that 0.2-0.3% of organic matter from deep sediments is organohalogens, and that there is a strong positive correlation between total organic carbon (TOC) and adsorbable organic halogen (AOX) in the pristine rivers and lakes in Sweden and Finland. Furthermore, monochloro-, dichloro-, and trichloroacetic acids are present in old snow and ice samples from Sweden, Norway, and the Antarctic.

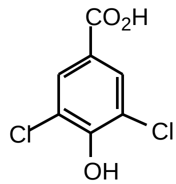
VII. Natural Soil Organochlorines

Recent years have witnessed a number of research investigations into the origin of organochlorine compounds that are found in soil, sediments, and surface waters. An excellent overview of these studies is provided by the 1995 Euro Chlor publication "The Natural Chemistry of Chlorine in the Environment."

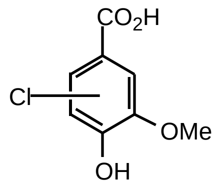
Commercially available humic acid is chlorinated by chloride ions in the presence of chloroperoxidase and hydrogen peroxide (*56, 57*). This crucial experiment demonstrates that the environmental production of chlorinated humic acid is possible and highly probable, especially since chloroperoxidase was found in most soils examined (*58*). The subsequent leaching of this chlorinated material and/or degradation products, such as chlorophenols, into surface waters may explain the large quantities of natural AOX in the River Rhine (*59*). This mechanism may also explain the occurrence of chloroform in pristine ground waters that has been frequently reported (*60*). Moreover, the concentration of organically bound chlorine in soil from rural areas around the world is 30-800 ppm (*60*). More recently, the structures of these chlorinated humic acids are beginning to be identified (*61*). For example, chloroaromatics **58-62** have been identified in degraded samples of fulvic acid isolated from unpolluted waters (*61*). The degradation was achieved by protecting free phenolic groups as ethyl ethers before treating the fulvic acid with permanganate/H_2O_2, and then methylating the carboxylic acids.



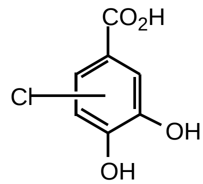
58



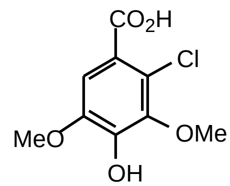
59



60



61



62

Unpolluted, humus-rich waters also contain relatively large amounts of 2,4,6-trichlorophenol and 2,4,6-trichloroanisole (*62*), and the former compound is a major reaction product in the phenolic fraction of the chloroperoxidase-mediated chlorination of humic substances (*63*).

Another possible route to chlorinated humic substances is an enzyme-mediated incorporation of chlorophenols into humic acids. This process has now been demonstrated experimentally using horse radish peroxidase, and is accompanied by a significant polymerization of the chlorophenols (*64*).

It has been reported that sea salt aerosols upon irradiation in the presence of nonhalogenated organic compounds and nitrogen oxides gives rise to chloroacetones and phosgene (*65*). This provocative result lends credence to the proposal that chloride ion in sea salt spray can be oxidized to active chlorine leading ultimately to the formation of organochlorine compounds in the marine air (*65*, *66*).

VIII. References

1. For more information, contact Dr. Victor Turoski, Corporate Research and Development, James River Corporation, 1915 Marathon Avenue, Neenah, Wisconsin 54956-0899, USA; Internet: victor_turoski@email.jrc.com. FAX: 414-829-8399.
2. "Chlorine and Health," G.W. Gribble, American Council on Science and Health, Inc., New York, 1995. Copies are available ($3.85) from ACSH, 1995 Broadway, 2nd Floor, New York, NY, 10023-5860, USA; FAX 212-362-4919.
3. "Chlorine and Life — Present and Future of Chlorine Industry," L. Puigjaner, ed., Environmental Center, Chemical Engineering Department, E.T.S.E.I.B., Polytechnic University of Catalunya, Barcelona, Spain, 1995.
4. E.J. Hoekstra and E.W.B. De Leer, *Chem. Brit.* 127 (1995).
5. D.J. Faulkner, *Chem. Brit.* 680 (1995).
6. R. Coxeter, "Frog Joins Chemical Warfare," *Fortune* **131**, No. 8, 32 (1995).
7. (a) M.M. Mack, T.F. Molinski, T.D. Meloy, and I.N. Pessah, *Biophysical J.* **68**, A174 (1995). (b) M.M. Mack, T.F. Molinski, E.D. Buck, and I.N. Pessah, *J. Biol. Chem.* **269**, 23236 (1994).
8. For a recent study involving bastidins, see G.R. Pettit *et al.*, *J. Nat. Prod.* **58**, 680 (1995).
9. R. Steinbrecher, M. Jocher, M. Wiedemann, J. Slemr, and J. Hahn, Eurotrac Symposium '92, 299 (1993).
10. T. Ichiba, Y. Nakao, P.J. Scheuer, N.U. Sata, and M. Kelly-Borges, *Tetrahedron Lett.* **36**, 3977 (1995).
11. P.A. Searle and T.F. Molinski, *J. Org. Chem.* **60**, 4296 (1995).
12. U. Brambilla, G. Nasini, and O.V. de Pava, *J. Nat. Prod.* **58**, 1251 (1995).
13. W.D. Clark and P. Crews, *Tetrahedron Lett.* **36**, 1185 (1995).
14. A.C. Pinto, P.P.S. Queiroz, and W.S. Garcez, *J. Braz. Chem. Soc.* **2**, 25 (1991).
15. K. Krohn, A. Michel, U. Flörke, H.-J. Aust, S. Draeger, and B. Schulz, *Liebigs Ann. Chem.* 1099 (1994).
16. T. Ohta, A. Takahashi, M. Matsuda, S. Kamo, T. Agatsuma, T. Endo, and S. Nozoe, *Tetrahedron Lett.* **36**, 5223 (1995).

17. A. Takahashi, T. Agatsuma, M. Matsuda, T. Ohta, T. Nunozawa, T. Endo, and S. Nozoe, *Chem. Pharm. Bull.* **40**, 3185 (1992).

18. A. Takahashi, T. Agatsuma, T. Ohta, T. Nunozawa, T. Endo, and S. Nozoe, *Chem. Pharm. Bull.* **41**, 1726 (1993).

19. J. Pika and D.J. Faulkner, *Tetrahedron* **51**, 8189 (1995).

20. M. Murakami, K. Ishida, T. Okino, Y. Okita, H. Matsuda, and K. Yamaguchi, *Tetrahedron Lett.* **36**, 2785 (1995).

21. T. Kato, Y. Shizuri, H. Izumida, A. Yokoyama, and M. Endo, *Tetrahedron Lett.* **36**, 2133 (1995).

22. G.M. Bonetto, R.R. Gil, J.C. Oberti, A.S. Veleiro, and G. Burton, *J. Nat. Prod.* **58**, 705 (1995).

23. P. Ciminiello, E. Fattorusso, S. Magno, and M. Pansini, *J. Nat. Prod.* **58**, 689 (1995).

24. N.K. Gulavita, S.A. Pomponi, A.E. Wright, M. Garay, and M.A. Sills, *J. Nat. Prod.* **58**, 954 (1995).

25. Y. Venkateswarlu and R. Chavakula, *J. Nat. Prod.* **58**, 1087 (1995).

26. R.C. Cambie, A.R. Lal, M.R. Kernan, and P.R. Bergquist, *J. Nat. Prod.* **58**, 940 (1995).

27. T. Miyamoto, Y. Ebisawa, and R. Higuchi, *Tetrahedron Lett.* **36**, 6073 (1995).

28. X. Fu *et al.*, *J. Nat. Prod.* **58**, 1384 (1995).

29. C.E. Salomon, D.H. Williams, and D.J. Faulkner, *J. Nat. Prod.* **58**, 1463 (1995).

30. G. Bifulco, I. Bruno, R. Riccio, J. Lavayre, and G. Bourdy, *J. Nat. Prod.* **58**, 1254 (1995).

31. H. Li, S. Matsunaga, and N. Fusetani, *J. Med. Chem.* **38**, 338 (1995).

32. M.V. D'Auria, *et al.*, *J. Nat. Prod.* **58**, 121 (1995).

33. P.A. Searle and T.F. Molinski, *J. Am. Chem. Soc.* **117**, 8126 (1995).

34. S.E. Brantley, T.F. Molinski, C.M. Preston, and E.F. DeLong, *Tetrahedron* **51**, 7667 (1995).

35. M.J. Garson, M.P. Zimmermann, M. Hoberg, R.M. Larsen, C.N. Battershill, and P.T. Murphy, *Lipids* **28**, 1011 (1993).

36. N.M. Carballeira and J.R. Medina, *J. Nat. Prod.* **57**, 1688 (1994).

37. "Biohalogenation Symposium," Whistler Center for Carbohydrate Research, Purdue University, West Lafayette, Indiana, USA, September 25, 1995.

38. L.A. Marquez and H.B. Dunford, *J. Biol. Chem.* **269**, 7950 (1994).

39. W. Sun and H.B. Dunford, *Biochemistry* **32**, 1324 (1993).

40. A.F. Dexter and L.P. Hager, *J. Am. Chem. Soc.* **117**, 817 (1995).

41. J.R. Carney and K.L. Rinehart, *J. Nat. Prod.* **58**, 971 (1995).

42. J. Ishihara, N. Kanoh, and A. Murai, *Tetrahedron Lett.* **36**, 737 (1995).

43. J. Collén, A. Ekdahl, K. Abrahamsson, and M. Pedersén, *Phytochemistry* **36**, 1197 (1994).

44. R. Tokarczyk and R.M. Moore, *Geophys. Res. Lett.* **21**, 285 (1994).

45. M. Foldes, R. Munro, T.C. Sorrell, S. Shankar, and M. Toohey, *J. Antibiot. Agents Chemother.* **11**, 21 (1983).

46. Y. Aoki and H. Kashiwagi, *Chemotherapy (Tokyo)* **40**, 997 (1992).

47. P. Groves, M.S. Searle, J.P. Waltho, and D.H. Williams, *J. Am. Chem. Soc.* **117**, 7958 (1995).

48. L. Yu, S. Mah, T. Otani, and P. Dedon, *J. Am. Chem. Soc.* **117**, 8877 (1995).

49. R.M. Moore and R. Tokarczyk, *Geophys. Res. Lett.* **19**, 1779 (1992).

50. R. Clement and C. Tashiro, Abstract Dioxin '91, Research Park, NC, USA, 1991.

51. S. Vollmuth, A. Zajc, and R. Niessner, *Environ. Sci. Technol.* **28**, 1145 (1994).

52. L.G. Öberg, R. Andersson, and C. Rappe, *Organohalogen Compounds* **9**, 351 (1992).

53. C. Rappe, "The Natural Chemistry of Chlorine in the Environment," *Euro Chlor*, 1995, p. 21.

54. S. Hashimoto, T. Wakimoto, and R. Tatsukawa, *Chemosphere* **21**, 825 (1990).

55. A summer 1996 publication date is anticipated by Ann Arbor Press for this book on the symposium held in August 1995 in Chicago.

56. L. Carlsen and P. Lassen, *Org. Geochem.* **18**, 477 (1992).

57. A. Grimvall, K. Laniewski, H. Borén, S. Jonsson, and S. Kaugare, *Toxicol. Environ. Chem.* **46**, 183 (1994).

58. G. Asplund, J. Christiansen, and A. Grimvall, *Soil Biol. Biochem.* **25**, 41 (1993).

59. E.J. Hoekstra and E.W.B. de Leer, *Water Sci. Tech.* **29**, 133 (1994).

60. E.J. Hoekstra and E.W.B. de Leer, "Contaminated Soil '93," 215 (1993).

61. O. Dahlman, R. Mörck, P. Ljungquist, A. Reimann, C. Johansson, H. Borén, and A. Grimvall, *Environ. Sci. Technol.* **27**, 1616 (1993).

62. A. Nyström, A. Grimvall, C. Krantz-Rülcker, R. Sävenhed, and K. Akerstrand, *Water Sci. Technol.* **25**, 241 (1992).

63. F. Hodin, H. Borén, A. Grimvall, and S. Karlsson, *Water Sci. Technol.* **24**, 403 (1991).

64. P. Lassen, A. Randall, O. Jorgensen, P. Warwick, and L. Carlsen, *Chemosphere* **28**, 703 (1994).

65. C. Zetzsch and W. Behnke, *Ber. Bunsenges Phys. Chem.* **96**, 488 (1992).

66. W.C. Keene, A.A.P. Pszenny, D.J. Jacob, R.A. Duce, J.N. Galloway, J.J. Schultz-Tokos, H. Sievering, and J.F. Boatman, *Global Biogeochemical Cycles* **4**, 407 (1990).