

Disinfection, Sterilization, and Preservation

Fourth Edition

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Lea & Febiger

Philadelphia • London

1991

IODINE AND IODINE COMPOUNDS

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Iodine, a nonmetallic, essential element discovered in 1812 by the French scientist Courtois, was named by Gay-Lussac in 1814 after the Greek word meaning violet, which is the color of iodine vapor.

It is not found in elemental form in nature but occurs sparingly in the form of iodides in seawater from which it is assimilated by seaweeds, in Chilean saltpeter and nitrate-bearing earth, known as *caliche*, in brines from old sea deposits, and in brackish waters from oil and salt wells.

Besides the one stable isotope ^{127}I , there exist more than 30 artificial isotopes with half-life periods between 0.2 s and 1.57×10^7 years. Some of them form a dangerous constituent part of the uncontrolled emissions during nuclear accidents, whereas others are used in nuclear medicine (mainly ^{131}I (8.04 d) and ^{125}I (13.2 h)).

So far as is known, the first use of iodine in medical practice was as a remedy for bronchocele (Halliday, 1821). The first specific reference to the use of iodine in wounds was made in 1839 (Davies, 1839; Boinet, 1865). Iodine was officially recognized by the Pharmacopeia of the United States in 1830, specifically as *tinctura iodini* (tincture of iodine). The first fundamental papers with a scientific basis about the degerming efficiency of iodine were published from 1874 to 1881 by Davaine (Vallin, 1882). In 1874, he found iodine to be one of the most efficacious antiseptics, a notion that is still valid 120 years later. On the basis of Davaine's experiences, Koch experimented with the disinfecting effect of iodine against anthrax spores. His results are contained in a comprehensive paper entitled "Desinfektion" (Koch, 1881). In the meantime, the literature about the use of iodine as a disinfectant has expanded markedly. Clinicians and microbiologists described a great number of experimental data and clinical applications, which can be found in numerous surveys (Reddish, 1957; Sykes, 1972; Bolek et al., 1972; Horn et al., 1972, 1974; Knolle, 1975; Gershenfeld, 1977).

Despite the successes that have been achieved with iodine, it was ascertained early that it also possesses

properties unsuitable for practical application. Goebel (1906) referred to the fact that iodine has an unpleasant odor; in addition, it stains the skin with an intense yellow-brownish color, causes blue stains in the laundry in the presence of starch, and combines with iron and other metals. Furthermore, its solutions are not stable, it irritates animal tissue, and it is a poison. The adverse side effects of iodine, its painfulness on open wounds, and the possibility of allergic reactions have in the past 100 years led to the production of a great many iodine compounds (and iodine preparations), with the aim of avoiding these incompatibilities without a significant loss of germicidal efficiency. In this connection, the iodophors finally succeeded as ideal forms of application.

CHEMISTRY

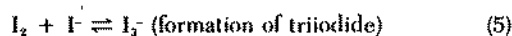
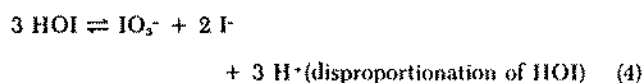
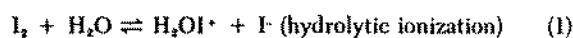
Iodine, the halogen with the highest atomic weight (126.9) of the common halogens, forms grayish-black metallic scales that melt at 113.5°C to a black mobile liquid. Iodine boils at 184.4°C at atmospheric pressure to produce the characteristic violet-colored vapor. In spite of the high boiling point, it already has an appreciable vapor pressure at room temperature and sublimates before it melts if it is not heated too fast and with too high a degree of heat.

Elemental iodine is only slightly soluble in water (0.334 g, i.e., 1.315×10^{-3} M/L at 25°C), forming a brown solution. Its solubility in water is increased with the addition of alkali iodides by which triiodides (and higher polyiodides) are formed (see Equation 5 following). In polar organic solvents (alcohols, ketones, carbonic acids), iodine dissolves with a brown color, in apolar solvents (CCl_4 , benzene, hydrocarbons) with a violet color. Whereas in the violet solutions, iodine is present as I_2 molecules (as in the gas phase), the brown color is explained by the formation of a compound between iodine and the solvent molecule (charge transfer complexes).

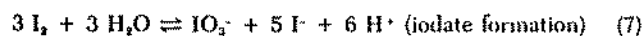
Iodine in Aqueous Solution

Compared with chlorine and bromine, the system I_2 - H_2O is much more complex. One of the reasons is the disproportionation of the hypohalous acid (see Equation 4 following), which, in the case of HOI, occurs at room temperature with appreciable speed, whereas in the case of HOCl and HOBr, elevated temperatures are necessary. Another reason is the high affinity of molecular iodide to iodide, resulting in the formation constant of the triiodide ion (see Equation 5 following) being considerably higher than those of Cl_3^- and Br_3^- ($K_{Cl_3^-} = 0.12$; $K_{Br_3^-} = 19$; $K_{I_3^-} = 800$ at $20^\circ C$). In aqueous iodine solutions, therefore, the formation of the triiodide ion (and to a small extent also of the pentaiodide ion, $I_5^- + I_2 \rightleftharpoons I_5^-$) is an important reaction that greatly affects the chemical behavior of this halogen. Finally, in iodine solutions the cationic species H_2OI^+ is present, whereas the corresponding chlorine and bromine cations are not able to exist (Bell and Celles, 1951).

The chemistry of aqueous iodine solutions is usually described with the following equations:



Whereas Equations 1, 2, 3, and 5 describe well defined and investigated elementary reactions, Equation 4 is an empiric formula that says nothing about the reaction mechanism and the iodous acid, HIO_2 , which is to be expected as an intermediate reaction product and whose chemical and bactericidal behaviors are not known. Equations 1 and 2, as well as 1, 2, and 4, are usually combined and written as 6 and 7, respectively:



In pure aqueous iodine solutions, therefore, at least seven different ions or molecules are present, of which molecular iodine (I_2), the hypoiodic acid (HOI), and the iodine cation (H_2OI^+) are supposed to have strong germicidal properties (Black et al., 1968; Krusé et al., 1970). However, the concentration of the iodine cation is so low—at conditions relevant to disinfection more than four powers below the HOI concentration—that it plays virtually no role in disinfection processes (Chang, 1971; Cottardi, 1978a).

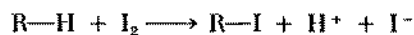
The same is the case with the hypoiodite ion, which becomes important only at $pH > 9$ and in the absence of iodide. Because at these conditions the disproportiona-

tion of iodate takes place very fast and therefore is avoided in disinfections, hypoiodite can be neglected as a contributor to microbicidal processes.

The tri-iodide ion (I_3^-), a major constituent in all iodide-containing preparations such as Lugol's solution, iodine tincture, and iodophor preparations is, compared to the free molecular iodine, only a weak oxidant and exhibits therefore only an inferior antibacterial activity, whereas the iodide ion (I^-) is without any effect (Kramer et al., 1952). Iodate (IO_3^-) is an oxidant only at pH values less than 4 and therefore has no effect on conditions where disinfections normally are carried out.

Calculations on the equilibrium concentrations show that at pH values less than 9 and at a total iodine concentration $\leq 10^{-4}$ M/L (25.4 mg/L), the sum $[I_2] + [HOI]^*$ of freshly prepared pure iodine solutions comes to over 97% of the total concentration (Table 8-1). The amount of OI^- and I_3^- ions can thus be neglected, with an oxidation capacity nearly present in the form of the bactericidal species I_2 and HOI (Cottardi, 1978a).

Although a differing behavior of I_2 and HOI has been observed against certain germs (Chang, 1971), in the pH range of 3 to 9 a more or less constant bactericidal activity of iodine in aqueous solution can generally be expected. This is in contrast to chlorine and bromine, where already at pH 8 the weak disinfecting hypohalite ions are present in appreciable amounts (Table 8-2). However, the ratio of $[HOI]$ to $[I_2]$ at a certain temperature ($25^\circ C$), as recorded in Tables 8-1 and 8-2, is governed not only by the pH value and total concentration, but also by the presence of substances that can interfere with the equilibria of Equations 1 through 7. In this latter connection, the iodide ion, I^- , is of primary importance: It emerges on the one hand at the hydrolysis of iodine (See Equations 1 and 6) and on the other hand at the reaction of iodine with organic material (except the addition to olefinic double bonds):



This additional I^- is always present in disinfecting solutions containing iodine and organic material and, as is seen in Table 8-3, may influence the ratio as well as the sum of $[HOI]$ and $[I_2]$, the sum however being rather constant in the selected pH-range.

Table 8-3 shows that the stabilizing effect of the iodide (as to the pH dependence of the percentual proportion of the different iodine species) increases with its concentration. Therefore in Lugol's solution ($C_{I_2} = 0.197$ M/L, $C_{I^-} = 0.602$ M/L) the portion of $[I_2]$ and $[I_3^-]$ (0.34 resp. 99.66%) remains constant even up to pH 10, indicating that this disinfectant is virtually pH-independent. The values of Table 8-3 can be summarized as is done in Figure 8-1, which shows that only at iodide concentrations greater than 10^{-4} M/L a noticeable decrease of the sum $[I_2] + [HOI]$ is to be expected. In spite of the wide range of iodine concentration (10^{-6} - 10^{-3} M/L) and pH (3 to 9) there is only a small variation

*[] means equilibrium concentration of the bracketed species.

Table 8-1. Equilibrium Concentrations* of I_2 , HOI, OI^- and I_3^- in 10^{-6} to 10^{-3} M Iodine Solutions at pH 3 to 9 and 25°C (in % of the Total Concentration)

pH	10^{-6}				10^{-5}				10^{-4}				10^{-3}			
	I_2	HOI	OI^-	I_3^-	I_2	HOI	OI^-	I_3^-	I_2	HOI	OI^-	I_3^-	I_2	HOI	OI^-	I_3^-
3.0	97.7	2.3	—	—	99.3	0.7	—	—	99.7	0.3	—	—	99.9	0.1	—	—
4.5	87.7	12.3	—	—	95.9	4.1	—	—	98.6	1.4	—	—	99.2	0.5	—	0.3
6.0	48.7	51.3	—	—	79.1	20.8	—	0.1	92.2	7.3	—	0.5	95.8	3.0	—	1.2
7.5	5.2	94.7	0.1	—	29.2	70.6	0.1	0.1	64.4	34.1	—	1.5	79.8	14.8	—	5.4
9.0	0.2	97.6	2.2	—	1.7	96.0	2.2	—	13.2	84.0	1.9	0.8	37.1	50.7	1.2	11.0

*Calculated after Cottardi, 1980.

Table 8-2. Comparison of the Equilibrium Concentrations* of Aqueous Solutions of Chlorine, Bromine, and Iodine ($C = 4 \times 10^{-6}$ M/L, i.e., 0.3 PPM Chlorine, 0.64 PPM Bromine, 1 PPM Iodine) at pH 3 to 9 and 25°C (in % of the Total Concentration)

pH	Iodine				Bromine			Chlorine		
	I_2	HOI	OI^-	I_3^-	Br_2	HOBr	OBr	Cl_2	HOCl	OCl^-
3.0	98.8	1.2	—	—	32.1	67.9	—	—	100.0	—
4.5	93.7	6.3	—	—	2.1	97.9	—	—	100.0	—
6.0	69.3	30.5	—	0.1	0.1	99.7	0.2	—	97.1	2.8
7.5	16.4	83.5	0.1	—	—	93.5	6.5	—	52.0	48.0
9.0	0.7	97.0	2.2	—	—	31.4	68.6	—	3.3	96.7

*Calculated after Cottardi, 1980.

Table 8-3. Equilibrium Concentrations* of I_2 , HOI, OI^- and I_3^- in 10^{-6} , 10^{-5} , 10^{-4} and 10^{-3} M Iodine Solutions Containing Additional Iodide (10^{-5} , 10^{-3} , and 10^{-1} M/L) at pH 3 to 9 and 25°C (in % of the Total Concentration)

C_{I_2}	C_{I^-}	pH	0				10^{-5}				10^{-3}				10^{-1}			
			I_2	HOI	OI^-	I_3^-	I_2	HOI	OI^-	I_3^-	I_2	HOI	OI^-	I_3^-	I_2	HOI	OI^-	I_3^-
10^{-6} M/L (0.25 ppm)	3	3	97.7	2.3	—	—	99.3	—	—	0.7	58.0	—	—	42.0	1.4	—	—	98.6
		4.5	87.7	12.3	—	—	99.1	0.2	—	0.7	58.0	—	—	42.0	1.4	—	—	98.6
		6.0	48.7	51.3	—	—	94.2	5.1	—	0.7	58.0	—	—	42.0	1.4	—	—	98.6
		7.5	5.2	94.7	0.1	—	38.0	61.6	—	0.4	57.4	1.1	—	41.5	1.4	—	—	98.6
		9	0.2	97.6	2.2	—	1.9	95.8	2.2	—	43.1	25.0	0.6	31.3	1.4	—	—	98.6
10^{-5} M/L (2.5 ppm)	3	3	99.3	0.7	—	—	99.3	—	—	0.7	58.1	—	—	41.9	1.4	—	—	98.6
		4.5	95.9	4.1	—	—	99.1	0.2	—	0.7	58.1	—	—	41.9	1.4	—	—	98.6
		6	79.1	20.8	—	0.1	94.3	4.9	—	0.7	58.1	—	—	41.9	1.4	—	—	98.6
		7.5	29.2	70.6	0.1	0.1	46.6	52.8	—	0.5	57.5	1.0	—	41.5	1.4	—	—	98.6
		9	1.7	96.0	2.2	—	0.3	94.4	2.2	—	43.5	24.5	0.6	31.4	1.4	—	—	98.6
10^{-4} M/L (25.4 ppm)	3	3	99.7	0.2	—	—	99.3	—	—	0.7	59.0	—	—	41.0	1.4	—	—	98.6
		4.5	98.6	1.4	—	—	99.1	0.2	—	0.7	59.0	—	—	41.0	1.4	—	—	98.6
		6	92.2	7.3	—	0.5	95.1	4.0	—	0.9	59.0	—	—	41.0	1.4	—	—	98.6
		7.5	64.4	34.1	—	1.5	67.7	30.4	—	1.9	58.3	1.1	—	40.6	1.4	—	—	98.6
		9	13.1	84.1	2.0	0.8	14.2	82.9	1.9	1.0	43.5	24.7	0.6	31.3	1.4	—	—	98.6
10^{-3} M/L (254 ppm)	3	3	99.9	0.1	—	—	99.6	—	—	0.4	67.3	—	—	32.7	1.4	—	—	98.6
		4.5	99.2	0.5	—	0.3	99.2	0.2	—	0.5	67.3	—	—	32.7	1.4	—	—	98.6
		6	95.8	3.0	—	1.2	96.0	2.5	—	1.5	67.2	0.1	—	32.7	1.4	—	—	98.6
		7.5	79.8	14.8	—	5.4	80.0	14.4	—	5.6	65.6	1.7	—	32.7	1.4	—	—	98.6
		9	37.1	50.7	1.2	11.0	37.3	50.3	1.2	11.2	43.5	25.6	0.6	30.2	1.4	—	—	98.6

*Calculated after Cottardi, 1980.

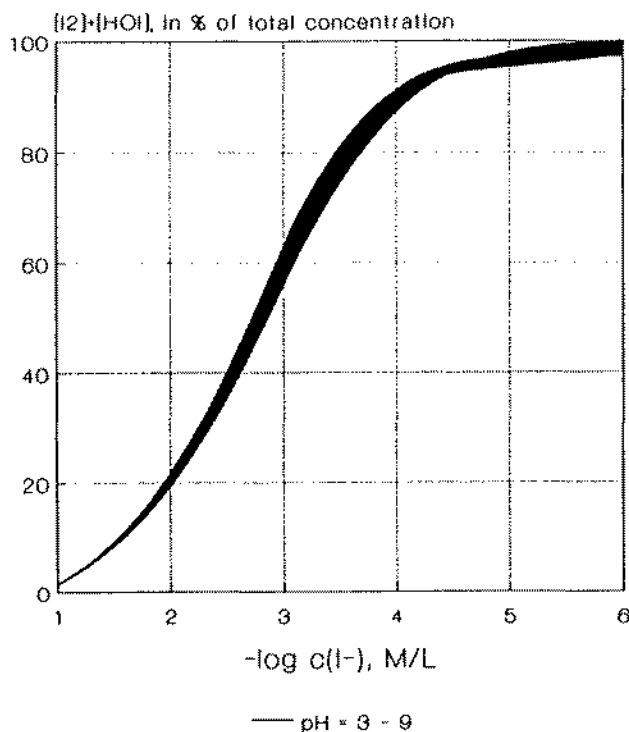


Fig. 8-1. Influence of the iodide concentration on the sum $[I_2] + [HOI]$ in aqueous iodine solutions. $C(I_2) = 10^6 - 10^{-3} M$ resp. 0.254 - 254 mg/L; pH = 3.0 to 9.0.

in the calculated percentual equilibrium concentrations, causing a slight broadening of the curve, so that Figure 8-1 allows one to estimate the percentual amount of the sum $[I_2] + [HOI]$ at a given iodide concentration and, because the concentration of OI^- can be neglected (it is only of importance at pH >9), the amount of triiodide, I_3^- , being the difference to 100%.

Stability of the Iodine-Water System

Iodine, like other disinfectants based on halogens in the oxidation states 0 or +1, as far as they are not present as pure substances (i.e., without a solvent), can gradually lose a part of their degerming properties (e.g., during storage). This is due to (1) substitutions of covalent hydrogen, e.g., O-H, N-H, C-H (as a result of the reaction with solvent molecules like H_2O , $EtOH$, and others), (2) additions to olefinic double bonds, and (3) the disproportionation of the hypohalous acid to halate in aqueous preparations (Equations 4 and 7, respectively), which has no degerming properties (see previous section). Although substitutions, which in the case of iodine are considered to be fewer than with chlorine and bromine, and additions can be avoided by an appropriate composition, the equilibria 1 through 7 are established in any case if water is present; as a consequence the inactive iodate also can be formed.

On the basis of calculated equilibrium concentrations and reaction times, the following conclusions have been

drawn concerning the stability (with regard to iodate formation) of iodine-containing disinfecting agents (Gottardi, 1981):

1. Below pH 6, a decrease of disinfecting effectiveness due to the formation of iodate can be excluded.
2. Above pH 7, the formation of iodate, whose extent largely depends on the pH value as well as on the iodide concentration, must be regarded carefully. Raising the pH value lowers the stability (iodate formation increases), whereas raising the iodide concentration improves the stability (iodate formation is reduced).
3. Because of the stabilizing effect of the iodide ion, provided that its concentration is high enough, the opposite effect of the pH value can be overcompensated for, and as a result of this, iodine-containing agents can also exhibit sufficient stability for practice in the weak alkaline range (pH less than 9).

In highly diluted iodine solutions (less than $10^{-5} M/L$, resp. 2.54 mg/L) which are present in disinfections of potable water or swimming-pool water, only a slow iodate formation can be expected even at pH 9 (Gottardi, 1978a). In accordance with this, in disinfection plants on an iodine basis, no significant iodate amounts have been detected (Black et al., 1968).

Effect of Organic Material

Iodine (like chlorine and bromine) reacts not only with living microorganisms but also with dead ones and with dissolved proteins. In the course of these complex reactions, halogen compounds emerge that have either a weaker degerming activity than the halogen originally used or none at all. The former are mainly compounds with N-halogen bonds, whereas the latter are those with C-halogen bonds and the halide ions.

With in-vitro experiments using peptone solutions, it was shown that iodine reacts with proteins at least three times slower than chlorine and nearly four times slower than bromine (Gottardi, 1976). Hence, in disinfection under conditions occurring in practice, i.e., in the presence of dissolved proteins (blood, serum, sputum), iodine is much more efficient than chlorine and bromine because the share of the employed halogen concentration that is available for the actual degerming reaction is considerably greater. The comparatively low reactivity with proteins, which is sufficient, however, to kill a living germ, and the virtual independence of the disinfecting activity of the pH value are the main reasons for the excellent degerming properties of iodine.

Mode of Action of Iodine as a Microbicide

Iodine, mainly in its molecular form, is able to penetrate the cell wall of microorganisms rapidly (Chang, 1971). Although exact details about the killing of a living cell by the I_2 molecule (or one of the reaction products occurring in aqueous solution) are not known, it can be assumed that iodine reacts

1. With basic N-H functions that are parts of some

amino acids (e.g., lysine, histidine, arginine) and the bases of nucleotides (adenine, cytosine, and guanine) forming the corresponding N-iododerivatives. By this reaction, important positions for hydrogen bonding are blocked, and a lethal disorder of the protein structure may occur.

2. By oxidizing the S-H group (Krusé et al., 1970) of the amino acid cysteine, through which the ability of connecting protein chains by disulfide (—S—S—) bridges, as an important factor in the synthesis of proteins, is lost.
3. With the phenolic group of the amino acid tyrosine, forming monoiododerivates or diiododerivates. In this case, the bulk of the iodine atom(s) in the ortho position may cause a form of steric hindrance in the hydrogen bonding of the phenolic OH group.
4. With the carbon-carbon double bond (C=C) of the unsaturated fatty acids. This could lead to a change in the physical properties of the lipids and membrane immobilization (Apostolov, 1980).

Annotation: Of these four points the second might be the most important, both because of the ubiquitous SH-groups and because of the very fast and irreversible reaction with iodine. The first point however is only of importance under alkaline conditions, which on grounds of stability (see previous section) are unusual at disinfections.

PREPARATIONS CONTAINING OR RELEASING FREE IODINE

Solutions of Iodine and Iodide

To this group belongs a great variety of preparations containing elemental iodine and potassium (or sodium) iodide in water, ethyl alcohol, and glycerol, or in mixtures of these solvents. They rank with the oldest disinfectants and have survived nearly 150 years on the basis of efficacy, economy, and stability. The following are official preparations according to USP XXI: (1) Iodine Topical Solution, an aqueous solution containing 2.0% iodine and 2.4% sodium iodide; (2) Strong Iodine Solution (Lugol's Solution), an aqueous solution containing 5% iodine and 10% potassium iodide; (3) Iodine Tincture containing 2.0% iodine and 2.4% sodium iodide in aqueous ethanol (1:1); and (4) Strong Iodine Tincture containing 7% iodine and 5% potassium iodide in 95% ethanol. Because all of these preparations contain large amounts of iodide (0.16 to 0.6 moles/L) the equilibria 1, 4, 6, and 7, which all contain iodide, are displaced far to the left side so that only the triiodide equilibrium 5 becomes important. As a result of this, these solutions virtually contain only iodine, iodide, and triiodide and are therefore very stable because there is no HOI or OI⁻ present that can undergo disproportionation to iodate (Equation 4). Because of their high content of free molecular iodine (e.g., Lugol's solution: [I₂] = 170 ppm) they are powerful disinfectants with the disadvantage of staining—and in some cases irritation—of living tissues.

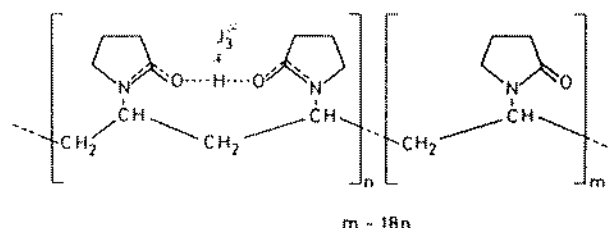


Fig. 8-2. Structure of solid povidone-iodine. After Schenck, H. U., Simak, P., and Haedicke, E. 1979. Structure of polyvinylpyrrolidone-iodine (povidone-iodine). *J. Pharm. Sci.*, 68, 1505-1509.

Preparations Containing Iodine, Iodide, and Organic Complexing Agents

Besides preparations with complexing agents of low molecular weight, such as tetraglycine hydroperiodide (Gershenfeld, 1977) or the inclusion compound iodine-maltosylcyclodextrin (Kawakami et al., 1988), this group includes the important "iodophors," whose name indicates generally the combination of iodine with a carrier (as these complexing agents usually are called) of high molecular weight. In aqueous solution, iodophors form the same iodine species as do the pure iodine solutions; however, the polymer carriers, because of their complexing properties, partly reduce the equilibrium concentrations of the iodine species and give the iodophor preparations properties that make them superior in some respects to solutions containing only iodine and iodide.

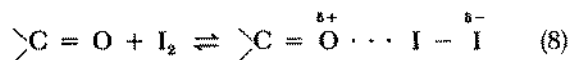
Iodophors

An iodophor is a complex of elemental iodine or triiodide with a carrier that has at least three functions: (1) to increase the solubility of iodine, (2) to provide a sustained-release reservoir of the halogen, and (3) to reduce the equilibrium concentration of free molecular iodine. The carriers are neutral polymers, such as polyvinyl pyrrolidone, polyether glycols, polyvinyl alcohols, polyacrylic acid, polyamides, polyoxyalkylenes, and polysaccharides.

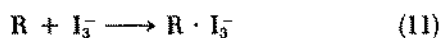
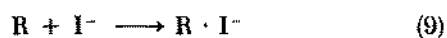
In the solid state iodophors form crystalline powders of a deep brown to black color, which in general do not smell of iodine, indicating a tight bonding with the carrier molecules. Their solubility in water is good but depends on the chain length of the polymeric molecules and varies in the case of povidone-iodine between 5% (type 90/04, average molecular weight near 1,000,000) and more than 20% (type 17/12, average molecular weight near 10,000). The best known iodophor is povidone-iodine, a compound of 1-vinyl-2-pyrrolidone polymer with iodine, which according to USP XXI contains not less than 9.0% and not more than 12.0% available iodine. On the basis of spectroscopic investigations (Schenck et al., 1979), it was found that povidone-iodine (in the solid state) is an adduct not with molecular iodine (I₂) but with hydrotriiodic acid (HI₃), where the proton is fixed via a short hydrogen bond between two carbonyl groups of two pyrrolidone rings and the triiodide anion is bound ionically to this cation (Fig. 8-2).

Aqueous Solutions of Iodophores. The chemistry of the aqueous solutions of iodophores is still more complex than that of pure iodine solutions, because the polymeric organic carrier molecules interact with the iodine species created by the reactions of Equations 1 through 5, which can cause a considerable change in their equilibrium concentrations.

As far as the chemistry of aqueous disinfectant solutions containing iodophores is understood today, both electronic and steric effects are responsible for this interaction (Gottardi, 1985). Thus, taking the known interactions with low molecular oxygen compounds such as amide, ester, ketone, and ether (Haruka Yamada and Kunio Kozima, 1960; Schmulbach and Drago, 1960) as an analogy, it can be assumed that, between molecular iodine and the iodophor molecules, which without exception contain such functional oxygen-containing groups (e.g., povidone: carbonyl oxygen of the amide function in the pyrrolidone ring), donor-acceptor complexes are formed, with iodine playing the part of the acceptor:



Furthermore, the iodophors, especially when in high concentrations, because of the spatial arrangement of the dissolved polymer molecules (near regions with helix-like structure) (Horn and Ditter, 1984), are obviously able to surround the free iodine forms in the manner of clathrates and withdraw it from the equilibrium (Equations 9 through 11). This interaction must be of importance for the iodide ion and above all for the large-mass triiodide ion, because in this case the formation of a donor-acceptor complex is not possible on grounds of the negative charge.



R = structural regions of the iodophor molecule capable of forming complexes by steric effects

These two effects, together with the equilibria 1 through 5, result in the content of the free molecular iodine being greatly reduced in disinfection preparations containing iodophor molecules (10% aqueous solution of povidone-iodine: $C_{\text{I}_2} \approx C_{\text{I}^-} \approx 0.04$ M/L, $[\text{I}_2] \approx 10^{-5}$ M/L, resp. 2.54 ppm), in comparison with pure aqueous solutions with the same total iodine and total iodide content (aqueous iodine solution, $C_{\text{I}_2} = C_{\text{I}^-} = 0.04$ M/L, pH 5: $[\text{I}_2] = 6.8 \times 10^{-3}$ M/L, resp. 1727 ppm*). The high content of free iodide (which varies between 10^{-3} and 10^{-1} M/L, according to the preparation) also means that HOI can be disregarded (see equilibrium), and only I_2

* Because the solubility of iodine lies at 334 ppm (25°C), the calculated value of 1727 ppm does not correspond with the actual equilibrium concentration. Therefore an aqueous solution of this composition will contain undissolved iodine.

is responsible for disinfection. For the description of the chemical conditions existing in aqueous iodophor solutions, therefore, besides the triiodide equilibrium (5), at least the equilibria 8 through 10 are necessary. Because in the latter case no thermodynamic constants are known, these conditions can be ascertained only in an empirical way.

The virtual absence of HOI means also that iodophor preparations are not impaired by a decrease of microbicidal power owing to the formation of iodate (see Equation 4). In spite of this, iodophor preparations are not fully stable because iodine attacks the organic carrier (and other components), a reaction ($\text{>C-H} + \text{I}_2 \longrightarrow \text{>C-I} + \text{I}^- + \text{H}^+$) which, by consuming iodine, reduces not only the reservoir of the available iodine, but also the concentration of the free molecular iodine, the latter being reduced to a greater extent, because iodide is produced too (see Equation 5; Gottardi, 1985). However, these iodine-consuming reactions occur at room temperature only very slowly, and can be compensated for by the addition of iodate in the form of the potassium salt, which, at an appropriate pH, oxidizes iodide to iodine (see Equation 7) at such a rate that the available and free molecular iodine of this preparation virtually remains unchanged for a long time.

The concentration of free iodine is largely independent of the pH value (pH 3 to 6), but changes considerably with the degree of dilution, when it passes through a maximum of $[\text{I}_2] \approx 10^{-4}$ M/L in the 0.1% solution.

As can be seen in Figure 8-2, the concentration of free iodine in a 10% povidone-iodine solution comes to approximately 2.0 mg resp. 8×10^{-6} M/L and rises in a 1:100 dilution nearly tenfold. On further dilution, after passing the maximum the free iodine behaves more and more "normally"—i.e., it decreases—and below 0.01% the povidone-iodine solution can be regarded as a simple aqueous solution of iodine. This "anomalous" behavior (which is a consequence of the different equilibria combined together), mainly the fact that the more concentrated an iodophore solution is, the less free iodine and therefore the less disinfecting power it has, must always be kept in mind when making experiments with this class of disinfectant. The low content of free molecular iodine in concentrated povidone preparations was obviously also the reason for the unexpected observation that some preparations didn't fulfill the requirement of auto-sterility. The isolated germs were of the species *Pseudomonas*, organisms that are known to be protected by matrices of biofilms, exhibiting in this way an extraordinary resistance against degerming agents. (For more details on this topic, see the chapter "Disinfection of Medical and Surgical Materials").

Another important feature of aqueous povidone-iodine solutions, shown by Figure 8-3, is that there exists a maximum concentration of nearly 10^{-4} M/L, resp. 25.4 mg/L of "free iodine" that arises in the approximately 0.1% solution and that can never be exceeded.

Because $[\text{I}_2]$ not only depends on the concentration of

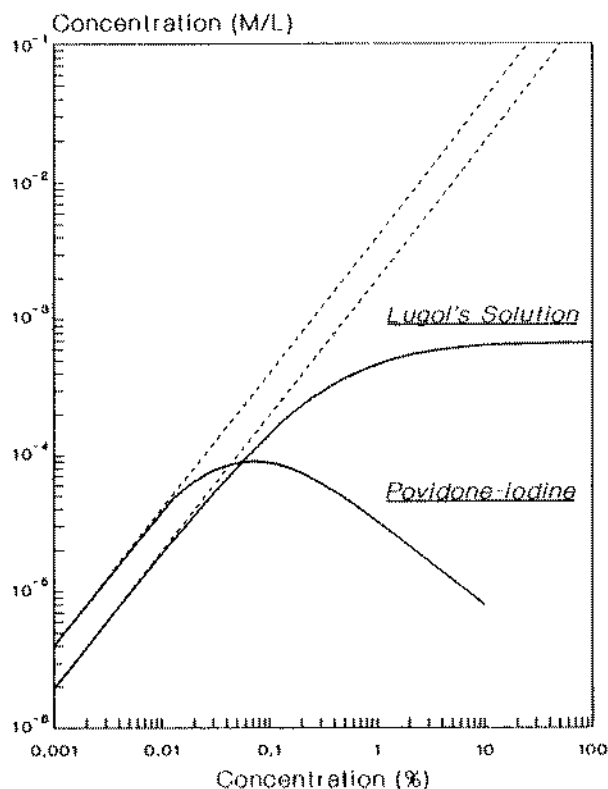


Fig. 8-3. Total available iodine (---) and free molecular iodine (—) in aqueous povidone-iodine (determined potentiometrically; Gottardi, 1983) and in Lugol's solution (calculated after Gottardi, 1980). Horn, D., and Ditter, W. 1984. Physikalisch-chemische Grundlagen der mikrobiziden Wirkung wässriger PVP-Iod-Lösungen. In *PVP-Iod in der Operativen Medizin*. Edited by G. Hierholzer and G. Görtz. Berlin, Springer.

povidone-iodine, but also on its total content of iodine and iodide which, as the specifications of the standard commercially available povidone-iodine show, undergoes considerable variations. Figure 8-3 only shows the typical course of $[I_2]$ as a function of the povidone-iodine concentration. Therefore the ordinate of the maximum (and to a lesser degree also its abscissa) in Figure 8-3 is not a constant for different iodophors and preparations containing iodophores.

Also in Figure 8-3 the behavior of Lugol's solution on dilution is shown, exhibiting the drastic reduction of free iodine caused by the complexing properties of the povidone molecules.

Influence of Temperature on the Concentration of Free Iodine. In a study about the concentration of free molecular iodine and its variation with temperature, nine commercial povidone-iodine preparations, as well as pure povidone-iodine solutions of different types and concentrations, have been investigated, setting forth the following results (Gottardi and Koller, 1986a): (1) The commercial products showed a remarkably great spread in the concentration of free iodine (0.2 to 10 ppm at 25°C), which may be attributed to their different compositions, especially the ratio of total iodine to iodide as

well as the kind and quantity of organic-pharmaceutical constituents. (2) All tested povidone-iodine systems showed a significant—and unexpectedly similar—change of the concentration of free iodine by the temperature. (3) The results concerning its relative alteration fit to an exponential function of the form

$$\Delta\% [I_2]_{\Delta t} = 100 [10^{0.023 \pm 0.0026/\Delta t} - 1],$$

which is valid from 10 to 40°C. Following this equation $[I_2]$ increases about 5.4 resp. 100% if the temperature rises about 1.0 resp. 13.1°C. (4) This increase of $[I_2]$ must be considered in the application of povidone-iodine preparations as disinfectants or antiseptics on living tissues. Because of their higher temperature (c. 30 to 36°C) the applied povidone-iodine preparations exhibit a significant higher $[I_2]$ than they do at room temperature ($\Delta t = 10-16^\circ\text{C}$: $\Delta\% [I_2] = 70$ to 130%). Therefore, a significant higher degerming efficiency also can be expected compared to in-vitro experiments, which are conducted in general at room temperature.

The Relevance of Free Molecular Iodine to the Efficiency of Iodophor Preparations. Although the iodophores as important pharmaceutical base materials in the solid state represent more or less defined chemical compounds (the main qualm for this statement concerns the variation in the chain length of the polymeric carrier molecules), they cannot be, strictly speaking, called bactericidal agents. The real bactericidal agent is the free molecular iodine, because it is this species alone for which a correlation between concentration and bactericidal activity has been proved (and not for the total iodine resp. iodophor concentration) (Berkelmann et al., 1982, Pinter et al., 1983, Gottardi and Puritscher, 1985).

The differing composition of pharmaceutical additives (such as detergents and back fatting agents), which all usually have iodine complexing properties, as well as the ratio of total iodine to total iodide (Pinter et al., 1983) that the preparations of the various manufacturers exhibit, result in great differences in the concentration of free molecular iodine in spite of the fact that the actual iodophor concentration resp. the concentration of the total (titrable) iodine might be the same. In this connection the determination of the free iodine—which can be done in three different ways: (1) by extraction with a nonpolar solvent, e.g., heptane (Pollack, 1985), (2) by dialysis (Horn and Ditter, 1984), and (3) by a potentiometric method (Gottardi, 1983)—is an important measure to get an indication of the bactericidal potency of the preparation. The total available iodine, however, which follows from the specification of preparation or simply can be assayed by titration, is a measure of the disinfection capacity. It comprises all oxidizing iodine species and should, therefore, not be mixed up with the free molecular iodine, which (except in highly diluted solutions) (see Table 8-3) amounts only to a small fraction of the total available iodine.

However, the importance of the concentration of the free iodine should not be overemphasized, because the commercially available iodophor preparations frequently contain other degerming constituents (e.g., alcohols) besides the iodine species; and on the other hand the pharmaceutical ingredients (e.g., detergents) may influence the susceptibility of a living germ for iodine, so that the

bactericidal rate does not always exactly correlate with the concentration of free iodine. Nevertheless, for preparations of similar composition the determination of free iodine is a reliable and simple means to make predictions of the bactericidal properties (Gottardi and Puritscher, 1986). (See also the chapter on disinfection of medical and surgical materials.)

Forms of Application. According to USP XXI the following application forms of povidone-iodine are approved: Povidone-Iodine Topical Solution, Povidone-Iodine Cleansing Solution, Povidone-Iodine Ointment, and Povidone-Iodine Topical Aerosol Solution. Concerning the available iodine, they have to contain not less than 85% and not more than 120% of the labeled amount. In general povidone-iodine preparations contain 1 to 10% povidone-iodine, which is equivalent to 0.1 to 1.0% available iodine. They may contain a small amount of alcohol (Topical and Cleansing Solution); the cleansing solutions contain one or more surface-active agents. The aerosol solution, however, is a povidone-iodine solution under nitrogen in a pressurized container.

The Influence of the Halogen Consumption on the Efficacy of Povidone Iodine Preparations. Because iodophores are mainly used as medical antiseptics the influence of iodine-consuming body fluids is a very important feature concerning bactericidal capacity and rate.

Although iodine, as mentioned above, is less likely to be consumed by proteinaceous substrates than bromine and chlorine are, its efficacy as a disinfectant is still reduced in certain antiseptic applications, where great quantities of reducible constituents (e.g., blood) are present, and which leads to the conversion of iodine into nonbactericidal iodide. Thus, not only is the reservoir of available iodine diminished, but the equilibrium of triiodide is influenced as well. Both of these effects cause a decrease in the proportion of free molecular iodine, the actual antimicrobial agent (Gottardi and Koller, 1986b).

When povidone-iodine preparations are contaminated with liquid substrata (e.g., blood) there is, in addition, the dilution effect characteristic of povidone-iodine systems that causes an increase in the equilibrium concentration of free molecular iodine (Fig. 8-3). To what extent this effect compensates for the other two effects depends on the content of reducing substances. Thus with whole blood, a large decrease in the concentration of free molecular iodine occurs, whereas in the presence of plasma, this concentration remains practically unchanged if the ratio is not too high (Gottardi and Koller, 1987).

The consumption phenomena that can be seen with whole blood, such as (1) the strong and practically spontaneous iodine reduction, (2) a decrease of the specific iodine consumption along with the increase of the blood volume, and (3) the poor reproducibility can, among other things, be attributed to the high content of reduced protein sulfure (-SH) of whole blood, and to the possibility of different reactions of iodine with SH-groups (oxidation to disulfides resp. sulfenic, sulfinic, and sulfonic

acids). It is important to note that in practice no substantial decrease of the bactericidal efficacy of 10% povidone-iodine preparations is likely to occur with body fluids having a composition similar to plasma (volume substrate/volume povidone-iodine 10% \leq 0.6). However, with whole blood this is indeed the case; therefore contamination by >25% full blood should be avoided.

Solid Microbicidal Compositions on Iodine Basis

To this group belong resins containing quaternary ammonium groups loaded with triiodide and higher polyiodide ions (e.g., pentaiodide). In contrast to the "classic" disinfectants, which contain antimicrobial agents that are dispersed in a liquid (or gas) phase, these resins rank among the "nonclassical chemical disinfectants" (NCCD), which consist of active moieties attached to, associated with, or stored (or a combination thereof) in a solid phase (Kril, Fitzpatrick, and Janauer, 1986). Their mode of action is explained either by direct, physical contact with their surface or by slowly releasing a disinfecting agent (in this case iodine) into the bulk phase being disinfected. Because the residuals of total iodine (I_2 and HOI) washed out by the water flowing through the resin are very low, the resins seem to be ideally suited for application in point-of-use and point-of-entry water purification units.

Preparations Producing Iodine in Connection with Water

Preparations of this kind do not contain elemental iodine, but rather iodide, and produce the former in a chemical reaction, which is started when iodide and an oxidant come in contact with water. "Heliogen," for example, is a mixture of chloramine-T, potassium iodide, and certain inert ingredients. The releasing of iodine can be generalized as



Preparations of this kind are marketed in the form of tablets or a powder, which can be used effectively as sanitizers. Other examples are the "Hio-Dine" process, which is used in swimming pool disinfection, with 1,3-dichloro-5,5-dimethylhydantoin as an oxidant (White, 1972), and a disinfection method published by Kinman and Layton (1976) using NH_2Cl as an oxidant.

N-Iodo Compounds

Because nearly all organic disinfectants on the basis of chlorine and bromine are N-chloro or N-bromo compounds, it is surprising that N-iodo compounds, which in aqueous solution release hypiodic acid ($\text{>N-I} + \text{H}_2\text{O} \rightarrow \text{>N-H} + \text{HOI}$), are not used in practice. In a study on the usability of N-iodo compounds as disinfectants, the following conclusions were drawn (Gottardi, 1978b).

Fresh and diluted aqueous solutions of N-iodo com-

pounds exhibit HOI concentrations corresponding to the sum of $[HOI] + [I_2]$ in pure iodine solutions of the same molarity, which let us expect similar bactericidal behavior of this class of compounds. Compared with iodine solutions, however, a higher rate of iodate formation and therefore less stability of this solution can be established, which is caused by the higher HOI concentration throughout. Under certain conditions (pH less than or equal to 7, concentration less than 10^{-5} M/L, normal interacting time), the stability should be sufficient for disinfecting purposes. Of particular interest is the possibility of investigating, in the virtual absence of molecular iodine, the bactericidal action of the HOI. Common practical use will depend on the costs, which are high as far as the purchasable N-iodo-succinimide is concerned. Hence, the N-iodo compounds should not be considered at present as an alternative to the more inexpensive elemental iodine.

Synopsis of Composition and Active Iodine Forms in Disinfectant Solutions Containing Iodine

Table 8-4 gives a synopsis of the different preparations containing resp. applications using iodine. Besides the total concentration of iodine and iodide, the presumable active species and their calculated, measured, or estimated equilibrium concentrations are shown. Furthermore a tentative description of the conditions in alcoholic solutions is given. In contrast to pure alcoholic solutions (containing only iodine and an alcohol), where iodine practically only occurs in the solvated molecular form, $I_2 \cdot ROH$, alcoholic preparations used in practice (Tincture and Strong Tincture of Iodine, USP XXI) also contain iodide and water, with the result that the equilibria 1 through 5 are established also. However, because of the iodide content, only the solvated iodine molecules ($I_2 \cdot ROH$ and $I_2 \cdot H_2O$, the latter being the "free mo-

lecular iodine"*)—apart from the alcohol itself—might be responsible as the active forms for disinfection. A differentiation between the two forms according to relative reactivity should turn out in favor of the hydrate complex because of the greater stability of the I_2 -alcohol-solvate complex (inductive effect of the alkyl group increases the electron-donating properties of the oxygen).

HOI as a virtual contributor to the microbicidal process is to be expected only in iodine/water systems of high dilution and low iodide concentration, as is the case of disinfection of drinking and swimming pool water (see also Table 8-3) on an iodine basis.

TOXICITY OF PREPARATIONS CONTAINING FREE IODINE

All preparations that contain elemental iodine have similar modes of action, not with qualitative but rather with quantitative differences. Preparations such as Strong Iodine Solution (Lugol's Solution, USP XXI), in which free molecular iodine is present in high quantities (170 ppm), of course have better degerming properties than an iodophor preparation that is designed to reduce, by complexing, the concentration of free molecular iodine, which normally comes to 2 to 10 ppm.

On the other hand, the toxicity of the free iodine for living tissue has to be considered. Impregnating healthy skin with Lugol's solution has no unpleasant effect, whereas the same agent applied to a large area of burned skin causes painful irritation. In this case, the application of a weaker disinfecting agent, e.g., an iodophor preparation, is preferred. With an increasing concentration of free iodine and an increasing capability of resorption of the treated body surface, the amount of iodine ab-

*The real free iodine (in the form of bare I_2 -molecules) occurs only in the gasphase, or in apolar solvents like CCl_4 , and is violet in colour, in contrast to $I_2 \cdot H_2O$ (and $I_2 \cdot ROH$), which causes a brown colour.

Table 8-4. Composition and Active Iodine Form in Disinfectant Solutions Containing Iodine

Components	Solvent	Examples	Total Iodine Content (total iodide content)	Iodine Form Mainly Responsible for the Microbicidal Effect (concentration proportion of the total iodine concentration)
I_2	Ethanol	Solution of iodine in alcohol	1%	$I_2 \cdot ROH$ (10,000 ppm*; 100%)
	H_2O	Drinking water, swimming pool iodination	10^{-5} – 10^{-6} M/L	I_2 aq, HOI ($[I_2] + [HOI]$): 0.25–2.5 ppm†; 98–100%)
I_2, I^-	H_2O	Lugol's solution	5% (10% KI)	I_2 aq (170 ppm†; 0.34%)
	Ethanol/ H_2O	Iodine tincture	2% (2.4% NaI)	$I_2 \cdot ROH$, I_2 aq
$I_2, I^-,$ polym. org. complexing agents‡, additives§	H_2O	Mucosal disinfectant and washing concentrates based on PVP-I	1–0.75% (iodide content varies greatly depending on the preparation)	I_2 aq (0.2–10 ppm‡; 0.003–0.1%)
	Propanol/ H_2O	Skin disinfectants (sprays)	0.1% (0.05%)	$I_2 \cdot ROH$, I_2 aq

*Estimated.

†Calculated (see Cottardi, 1981).

‡Measured potentiometrically (see Cottardi, 1983) in commercially available products.

§Povidone, polyoxyalkylenes, polyetheryglycols etc.

||Buffers, detergents, foam stabilizers, artificial colourings etc.

sorbed by the body also increases and manifests itself in the serum level of iodide. In general, therefore, the serum level rises less from the application of an iodophor than with iodine tincture or Lugol's solution (Knolle, 1975). On treating burns, Hunt et al. (1980) found that the amount of absorbed iodine was directly related to the size of the burn, and although clinical evidence of cell or organ toxicity is as yet undetermined, it seems that high serum levels of iodide imply toxicity. Kuhn et al. (1987) also state that on treating burns with a povidone-iodine preparation, plasma iodine (i.e., iodide) sharply increased; from 6.4 ± 0.4 to 20.7 ± 4.7 $\mu\text{g}/100$ mL, however, the authors hold that the thyroid function does not seem to be modified by plasma iodine overload.

In a large-scale study at an obstetric ward it was found that the iodine overload of the mothers, caused by skin disinfection prior to delivery using an iodophor preparation, induces a transient impairment of thyroid function of the infants, especially if breast fed. Because this situation is detrimental to screening for congenital hypothyroidism iodophor preparations are not recommended in obstetrics (Chanoine et al., 1989). High doses of free iodine, e.g., in form of iodine tincture, are highly toxic if brought into body cavities and cause swelling and bleeding of mucous membranes. Consumption of 30 g of iodine tincture can be fatal (Wirth et al., 1967). As an antidote for such accidents 10 to 20 g sodium thiosulfate (reduction of iodine to iodide) or starch (formation of inclusion compounds) per os are recommended (Kuschinsky and Lüllmann, 1984). Concerning the incorporation of iodine the following generalizations can be made:

1. Because the horny layer of the intact skin is an effective barrier against electrolytes (Goldsmith, 1983) it is penetrated by iodine in the form of molecular iodine and not of iodide.
2. In body cavities (at the treatment of mucous membranes, perineal wash, etc.) which are not protected by a stratum corneum, however, also the incorporation of iodide becomes important all the more that iodine preparations always contain iodide.
3. Depending on the chemical nature of the tissue iodine penetrates (dry skin with low, resp. surfaces of body cavities with high content of reducing substances), the absorbed iodine will be reduced more or less fast to iodide.
4. The amount of total iodine (I_2 and I^-) absorbed by the body mainly depends on
 - a. The concentration of free molecular iodine (and of iodide) of the preparation
 - b. The time of application
 - c. The treated area
 - d. The nature of the treated area.
5. As long as not reduced, i.e., free, iodine is present in the skin it will diffuse not only into deeper regions but also back (out of the skin), performing for a certain time a residual bactericidal activity on

the skin surface. The reduced portion, however, remains for some time in the body and gives rise to an increase of the level of serum-iodide.

6. The incorporated iodine in the form of iodide and organic bound iodine (which comes to ~75% of the total resorbed iodine) leaves the body by urinary excretion with a biologic half-life of approximately 2 days (Cloebel et al., 1984).

The main restraints against iodine preparations are based upon the suspicion of a possible disorder of thyroid functions caused by the iodine uptake. Cloebel et al. (1984) investigated iodine uptake after use of povidone-iodine preparations (Betaiodona) as mouth antiseptic, vaginal gel, and liquid soap in subjects with normal thyroid function. By measuring serum I^- , T_3 , T_4 , TSH, and urinary iodide excretion (as an index of thyroid function), the authors observed an increase in iodine supply of up to 2 mg daily, but in no case the developing of hyperthyroidism or hypothyroidism. Because the test conditions were drastic (e.g., hands and forearms were washed 10 times for $2\frac{1}{2}$ minutes with povidone iodine liquid soap within 5 hours) one would tend to think that povidone iodine preparations are nontoxic. However, taking into account that, as mentioned above, the iodine uptake depends—among other factors—on the concentration of free iodine of the used preparation, which in this case was not ascertained, the notion of nontoxicity strictly speaking applies only to the preparations used by the authors and the given application. Because the content of free molecular iodine at present needs not be specified and, what is more, varies considerably in commercially available preparations (Cottardi and Koller, 1986a), one should be careful in making generalizations.

RESIDUAL EFFECTS OF IODINE PREPARATIONS

The above-mentioned backdiffusion of the not-reduced portion of the absorbed iodine, which takes place much slower than the uptake, interestingly, has not been recognized until now. By means of a new photometric method this iodine flux ($[\text{dim}] = \text{mass}/\text{area} \cdot \text{time}$) has been ascertained on the skin after application of Lugol's solution and povidone iodine preparations with various concentrations of free iodine. The most important findings are the following: The intensity of the iodine flux depends on the amount of iodine absorbed by the skin, which as far as it is concerned depends on the concentration of free iodine of the applied solution and the time of application. Applying Lugol's solution (170 ppm free iodine) for only 1 minute, the flux could be detected for approximately 24 hours (range: 50 to 0.005 $\mu\text{g I}_2/\text{cm}^2 \cdot \text{min}$), whereas after application of a povidone iodine preparation (10 ppm) for 3 to 5 minutes the flux was detectable $\frac{1}{2}$ to 1 hour (range: 0.2 to 0.005 $\mu\text{g I}_2/\text{cm}^2 \cdot \text{min}$) (Cottardi, 1989).

The latter result suggests that even the application of iodophor preparations could give rise to a persistent (residual) microbicidal action. This has been proved by com-

paring the surviving CFUs of *Micrococcus luteus* (applied to the skin by artificial contamination) on normal skin as well as on skin that has been treated for 5 min with a povidone-iodine preparation (10 ppm free iodine) immediately before contamination. A logarithmic reduction rate of 0.4 was found, a result that confirmed the bactericidal action of the iodine diffusing out of the skin (Gottardi, in preparation).

As long as iodine diffuses out of the skin, so to speak, an active disinfection from the inner regions of the skin takes place; therefore an effective action on the residual germs can be expected, a feature that seems to be unique in the field of skin disinfection.

Regarding this, Hartmann (1985) found by a special method that the reduction of the total resident flora was significantly higher using povidone-iodine than it was with isopropanol. This is in contrast to the usual findings, mainly in testing preparations for surgical hand scrub, which exhibit in general a better degerming activity of alcohols.

ORGANIC IODINE COMPOUNDS

Compounds of this class contain iodine that is bound to a carbon atom. With regard to properties and mode of action as disinfectants, they differ from the previously described disinfectants in that they contain neither free iodine nor other oxidizing iodine species. In the case of iodoform (CHI_3), however, there exist contrary opinions, because on the one hand iodoform is supposed to produce elemental iodine and formaldehyde in connection with water (Knolle, 1975), while, on the other hand, it was impossible to detect any free iodine in an aqueous slurry of CHI_3 at 37°C and pH 7 with a method that is sensitive down to 5×10^{-8} M/L (Gottardi, unpublished).

Iodoform (triiodomethane), probably the oldest pharmaceutically used iodine compound, forms yellow crystals with a characteristic anesthetic odor. It came into extensive use as dusting powder, especially as a local anti-infective agent to promote granulation and diminish infections of open wounds (Gershenfeld, 1977). Because of its toxicity (it can cause such effects as sleeplessness, hallucinations, and spasms) it has been replaced by other preparations, especially those containing iodophors. The compound is not specified in the USP XXI.

Iodine derivatives of quinoline exhibit protozoacide and metazoacide properties and have shown excellent results in prophylactic and therapeutic use (Gershenfeld, 1977). Iodoquinol (USP XXI, 5,7-diodo-8-quinolinol) and Clioquinol (USP XXI, 5-chloro-7-iodo-8-quinolinol) are the best known active substances of this type and serve as the basis for creams, ointments, powders, and tablets. To this class of compounds belong also the iodine-containing x-ray contrast media. Examples are Iocetamic Acid, Iopanoic Acid, and Iothalamic Acid (all USP XXI). They contain a benzene ring system with three iodine atoms in meta-position, and are used as such but also in form of their derivatives. The radioactive compounds Iodohyppurate Sodium I 123 resp. I 131 (both USP XXI)

should also be mentioned, which are used for nuclear medical purposes.

Iodonium Compounds

This class has the general formula $[\text{R}_2\text{I}^+]\text{X}^-$ (where R is an organic radical and X⁻ an inorganic or organic anion) and is of more theoretic than practical interest. The structure resembles the onium compounds (e.g., quaternary ammonium), and the active part of these compounds is iodine in the oxidation state +3. Diphenyliodonium chloride, whose degerming properties have been investigated by Gershenfeld and Witlin (1948), appears to be the most generally effective substance.

PRACTICAL APPLICATIONS

Iodine as a Disinfectant in Human Medicine

The most important application of iodine in human medicine is the disinfection of skin, which has been in use since the mid-nineteenth century (Reddish, 1954). Besides prophylactic actions (e.g., the preoperative preparations of the skin, the surgical disinfection of hands, the disinfection of the perineum prior to infections and transfusions), iodine preparations are also used for therapeutic purposes, e.g., the treatment of infected and burned skin. The previously used aqueous iodine and tincture nearly 30 years ago have been replaced, to a great extent, by the iodophors, which cause less unwanted side reactions, such as staining, irritation of tissue, and resorption of iodine. Among the investigated iodophors, povidone-iodine has been described as the compound of choice (Knolle, 1975). However, attempts are made to replace the povidone carrier by other macromolecules, which might be still more harmless than povidone, which after all has been used as a blood substitute. In this connection polymers built up of sugar molecules (e.g., polydextrose) are of great interest. When rigid aseptic precautions are required and no painful irritations are to be expected, however, iodine tincture is still in use as the strongest disinfectant based on iodine. A detailed review of the use of iodine in human medicine is given by Knolle (1975), and a good historical account and information on aqueous solutions of iodine and tincture is given by Reddish (1957).

Iodine has also been used for the disinfection of medical equipment, such as catgut, catheters, knife blades, ampules, plastic items, rubber goods, brushes, multiple-dose vials, and thermometers (Gershenfeld, 1977). It should be mentioned, however, that disinfection with iodine is not appropriate for every sort of material. Many metal surfaces in particular are not resistant to oxidation and can be altered. Furthermore, some plastics absorb elemental iodine, which causes a brownish staining.

Disinfection of Water

Drinking Water

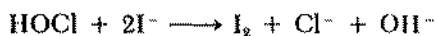
The first known field use for iodine in water treatment was in World War I by Vergnoux (White, 1972), who

reported rapid sterilization of water for troops. Since that time, several studies have been made (White, 1972) showing that iodination is suitable for the disinfection of drinking water, especially in case of emergency. Of considerable importance is the work of Chang and Morris (1953), which led to the development of tetraglycine hydroperiodide tablets ("Globaline"), which have been successfully used to disinfect small or individual water supplies in the U.S. Army. This method of water purification (addition of iodine tablets or calcium hypochlorite to the water, followed by a 25- or 30-minute disinfectant contact period, respectively, before drinking) is still in use in the U.S. Army. However one became also aware that this method of purification involves some health risks since the chemicals carrying out the disinfection are not removed at these procedures (Schaub, 1986). Black et al. (1965) have demonstrated, in two prison water systems, that iodine in doses up to 1.0 ppm is sufficient for disinfection, does not produce any discernible color, taste, or odor, and has no adverse effect upon the general health or thyroid function. Thomas et al. (1978) reported a pilot project with a 15-year duration in which they observed no instances of ill effect caused by the use of iodine for water disinfection. The authors found that iodination is an effective and economic means of water purification, of particular advantage in rural and underdeveloped countries.

Lately the iodine resins have been successfully used as a basis for purifier units, which, as long as they are not exhausted, work very well, bringing about a kill of 4 logs. For emergency and for travelers "pocket purifiers" have been developed whose performance was officially approved by being registered by the EPA (Regunathan and Beauman, 1986).

Swimming-Pool Water

The application of iodine to the treatment of swimming pools is an entirely different process from that of potable water treatment, because in the former, elemental iodine is applied directly to the water in crystal or possibly in tablet form, whereas in the latter, iodine is generally applied in the inert iodide form and later released as elemental iodine by coming in contact with an oxidant such as chlorine (White, 1972), as follows:



1,3-Dichloro-5,5-dimethylhydantoin, whose combination with iodide is known as "Ilio-Dine" process (designed especially for the disinfection of swimming pools), may also serve as an oxidant. It became apparent, however, that this N-chloro compound is not ideal because it decomposes in aqueous solution, forming undesirable end products (White, 1972).

Compared with chlorine, the use of iodine has the advantage that it reacts only to a small extent with ammonia or other nitrogenous compounds and therefore produces no compounds that are likely to contribute to swimmers' discomfort in the form of eye irritation or obnoxious odors (Black, 1961). The use of iodine in swim-

ming-pool disinfection has the following advantages (Putnam, 1961): (1) approximately one third saving on chemical cost, (2) no disagreeable odor or taste, (3) no irritation of the mucous membranes, (4) good disinfection of swimming-pool waters, (5) no danger in storage or use, because material is in crystalline form, (6) residual is stable and does not fluctuate quickly, (7) pH is stable after balance is reached, and (8) swimmers' comfort is protected.

On the other hand, iodine is a notoriously poor algicide, and the control of algae growth requires additional measures. Probably the most serious flaw in the use of iodine is the difficulty in controlling the color of the pool water, mainly in the presence of a large amount of iodide, which causes the development of yellowish-brown I_3^- ions. The problem of color control plus the inability of iodine to control algae all but eliminate it from use by the swimming-pool industry (White, 1972).

Wastewater

Only few contributions deal with the use of iodine in the disinfection of waters that, in contrast to drinking and swimming-pool water, do not come in direct contact with man, e.g., wastewater and industrial waters. Because these waters in general are highly charged with dissolved nitrogenous substances (proteins and their hydrolysis products), the use of iodine, with its only slight tendency to react with nitrogen compounds, should be of great advantage.

In applications, however, which range in technical dimensions, the question of cost also has to be considered, and because iodine is nearly three times as expensive as chlorine in price per mole, the advantages and disadvantages of iodine must be weighed carefully. In a study about a new method of disinfection with a mixture of I^- and NH_2Cl that generates elemental iodine Kinman and Layton (1976) find that this system offers considerable potential for use in water disinfection for potable waters, industrial waters, and waters that must be discharged to shellfish areas. Investigating alternatives to wastewater disinfection, Budde et al. (1977), in pilot plant studies, compared the disinfectants chlorine, ozone, and iodine, finding that for the same level of fecal coliform destruction, iodine was most costly under all conditions studied.

Disinfection of Air

Since Lombardo (1926) first advocated the use of iodine as an aerial disinfectant, experiments on the disinfection of air have been carried out, mainly during World War II. Plesch (1941) recommended the aerial disinfection of air-raid shelters with iodine vapors as a prophylactic measure against influenza. White et al. (1944) reported iodine to be effective as an aerial disinfectant at concentrations much below its saturation vapor pressure, and Raymond (1946) found a "relatively tolerable" concentration of 0.1 mg/lit³ (3.5 mg/M³) to be sufficient for a rapid kill of freshly sprayed salivary organisms. Since that time, however, no more publications have appeared concerning iodine as an air disinfectant.

Obviously, one is aware of the danger that iodine vapors pose to the respiratory organs, documented by the fact that the maximum allowed concentration of iodine comes to 1.0 mg/M³ (threshold limit value; Lewis and Sweet, 1986), which is less than one-third of the concentration recommended by Raymond (1946).

RANGE OF ACTION

Iodine is an excellent prompt effective microbicide with a broad range of action that includes almost all of the important health-related microorganisms, such as enteric bacteria, enteric viruses, bacterial viruses, and protozoan cysts (Hoehn, 1976). Mycobacteria and the spores of bacilli and clostridia can also be killed by iodine (Wallhäusser, 1978). Furthermore, iodine also exhibits a fungicidal and trichomonocidal activity (Knolle, 1975). As is expected, varying amounts of iodine are necessary to achieve complete disinfection of the different classes of organisms. Within the same class, however, the pub-

lished data on the disinfecting effect of iodine correspond only to a small extent. In particular, the published killing times of spores (Wallhäusser, 1978) and viruses (Knolle, 1975) are widely disparate. One reason for this might be the non-uniform sensitivity of microorganisms to iodine, which applies not only to the type of organism but also to the growth conditions. Pyle and McFeters (1989) could demonstrate that bacterial isolates (predominantly *Pseudomonas sp.*) from water systems disinfected by iodine showed differences (which had, however, not always the same sign) of up to 4 logs decrease after contact with iodine (1 mg/L, pH 7, 1 min) if grown in brain heart infusion or after cultivation in phosphate buffer.

As mentioned by Hoehn (1976), comparison of previously published references concerning effectiveness in disinfection processes of different microorganisms are difficult because of the myriad of different environmental conditions existing when experiments are conducted, e.g., pH value, temperature, concentration and type of iodine preparation, time of exposure to the disinfectant,

Table 8-5. Practical Applications of Iodine as a Disinfectant: Concentration, Exposure Time, Disinfective Result

Scope of Application	Concentration	Conditions	Exposure Time (Min)	Disinfective Result	References
Drinking water	8 ppm	—	10	"Kill of water-borne pathogens"	Committee on Medical Research, 1948
	3-4 ppm	25°C	12	"Reduces 10 ⁶ bacterial/mL to less than 10 bacterial/mL"	Chang and Morris, 1952
	3-4 ppm	3°C	22		
Drinking water in emergency	5-6 ppm	20-25°C	10	"Excellent disinfectant for water supplies under emergency conditions"	United States Public Health Service, 1940
	5-6 ppm	near 0°C	20		
	5 drops I ₂ -tincture to a quart of water	Clear water	30	"Water safe for drinking"	
	10 drops I ₂ -tincture to a quart of water	Cloudy water	30		
Swimming-pool water	4.0-8.0 mg/L	Turbid water of low quality	30	"Water of virtual potable quality"	Ellis and van Voce, 1989
	0.2 (0.1) ppm	—		"Provides water of satisfactory quality"	Black et al., 1959
	0.2 ppm	—		"Maintains the water at a satisfactory bacteriological quality"	U.S. Public Health Service, 1962
General germicidal action	1:20,000	Absence of organic matter	1	"Most bacteria are killed"	Goodman and Gilman, 1980
	1:20,000	Absence of organic matter	15	"Wet spores are killed"	Goodman and Gilman, 1980
	1:200,000	Absence of organic matter	15	"Will destroy all vegetative forms of bacteria"	Goodman and Gilman, 1980
Disinfection of skin	1% tincture	—	90 sec	"Will kill 90% of the bacteria"	Goodman and Gilman, 1980
	5% tincture	—	60 sec	"Will kill 90% of the bacteria"	Goodman and Gilman, 1980
	7% tincture	—	15 sec	"Will kill 90% of the bacteria"	Goodman and Gilman, 1980
	1% aqueous I ₂ -solution	Skin of hands	20 min	"Inactivation of rhinovirus"	Carter et al., 1980
	2% aqueous I ₂ -solution	Skin of hands	3 min	"Inactivation of rhinovirus"	Carter et al., 1980

and amount and type of dissolved organic and inorganic substances. Another problem is the fact that, in general, most of these conditions are not described in detail, and an exact comparison of the germicidal effectiveness of iodine against different organisms, as well as a comparison with the other halogens, is therefore virtually impossible. In spite of these difficulties, some authors have tried to summarize the disinfecting properties of iodine and the other halogens by reviewing the literature and analyzing the existing data. The most important conclusion is that a residual of 14.6 ppm, respectively (Chang, 1971).

2. On a weight basis, iodine can inactivate viruses more completely over a wide range of water quality than other halogens (Krusé, 1970).
3. In the presence of organic and inorganic nitrogenous substances, iodine is the cysticide of choice because it does not produce side reactions that interfere with its disinfecting properties (Krusé, 1970).
4. Iodine would require the smallest mg/L dosage compared to chlorine or bromine to "break any water" to provide a free residual (Krusé, 1970).
5. I_2 is two to three times as cysticidal and six times as sporocidal as HOI, whereas HOI is at least 40 times as virucidal as I_2 . This behavior is explained on the one hand by the higher diffusibility of molecular iodine through the cell walls of cysts and spores and on the other hand by the higher oxidizing power of HOI (Chang, 1971).
6. For some microorganisms an iodine resistance also has been ascertained, e.g., *Pseudomonas alcaligenes* and *Alcaligenes faecalis*, which can account for the bulk of the microbial flora in iodinated swimming pools (Favero and Drake, 1966).
7. Because disinfection is a chemical reaction, the influence of temperature on reaction speed—as a rule of thumb lowering the temperature about 10° halves the speed—has to be considered at microbicidal events in such a way that either the contact time or the concentration of the disinfectant have to be increased if cold water has to be treated. The lack of efficiency at low temperatures was demonstrated by Regunathan and Beauman (1986), showing that some iodine preparations designated to purify canteen water worked well against *Giardia* at 20°C but not at 3°C if used according to the instructions.

A survey of concentration, exposure time, and disinfective result in practical applications of iodine is given in Table 8-5.

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