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POTENTIAL ENVIRONMENTAL CHEMICAL HAZARDS

PART III. INDUSTRIAL AND MISCELLANEOUS AGENTS

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INTRODUCTION

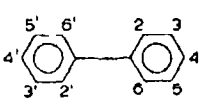
In the previous paper, the potential environmental chemical hazards related to drugs[1] and feed medicants and pesticides[2] were considered via an *a-priori* consideration of their chemical structure, nature of metabolites and degradation products with relation to known and hazardous insults and the inter-relationships and commonality of hazards present in various use categories. The present section focuses on industrial and miscellaneous agents in analagous consideration.

Polymer and plastic ingredients

A wide variety of organic derivatives are used in the polymers and plastics industry as plasticizers, modifiers, emulsifiers, stabilizers and solvents, and their inertness and/or safety is far from being established.

Polychlorobiphenyls. Polychlorinated biphenyls (PCB's) are produced by various manufactures and are represented as "a series of inert, chemically resistant, fire-retarding plasticizers compatible with a wide variety of resins, varnishes, waxes and paints; they vary from mobile, oily liquids to white crystals and hard transparent resins"[3]. The series of Aroclors (Monsanto) are marketed under various numbers and consist of mixtures of chlorinated biphenyls and terphenyls. The 1200 series relates to the biphenyls, the 5400 series to the terphenyls, and the 4400 series to a mixture of bi- and terphenyls. The annual production of PCB's in the Western world till most recently was estimated at 100 million pounds.

In the commercial process for PCB manufacture, biphenyls are chlorinated with anhydrous chlorine with either iron filings or ferric chloride as the catalyst; the byproduct is hydrogen chloride and the product is a mixture of several PCB's. In the process of replacing hydrogen atoms with chlorine atoms, a large number of substitution combinations arise, *viz.*,



For example, three monochlorobiphenyl isomers are possible, 12 dichlorobiphenyl isomers, 21 trichlorobiphenyl isomers and so on. Theoretically, 210 compounds can be prepared by this substitution process (a typical PCB example would be 2,4,6,2',4'-pentachlorobiphenyl).

The chemical properties that make polychlorobiphenyls desirable industrial materials are their excellent thermal stability, their strong resistance to both acidic and basic hydrolysis and their general inertness. The largest single use of PCB's is related to their electrical properties, as coolant insulation fluids in transformers. Other uses of PCB's include impregnation of cotton and asbestos for braided insulations of electrical wiring, plasticizers of vinyl chloride polymer freons, a plasticizer in wire and cable coatings and in ballasts for fluorescent fixtures. Because of their thermal stability and fire resistance, the PCB's also find application in high-pressure hydraulic fluids, heat transfer agents, machine tool cutting oils, specialized lubricants and gasket sealers. Miscellaneous uses include; formulation into epoxy paints, protective coatings for wood, metal and concretes; adhesives and in carbonless reproducing paper; and as plasticizers in plants, resin and chlorinated rubber and have been recommended for improving lindane residues[4]; they have also been shown to increase the insecticidal properties of DDT.

Polychlorinated biphenyls along with DDE [1,1-dichloro-2,2-bis (*p*-chlorophenyl) ethane] are reported to be the most abundant of the chlorinated aromatic pollutants in the global ecosystem[5].

Extracts from tissues of sea eagles, pike and salmon[5] as well as in various species of British wildlife[6] contained PCB's and in the latter instance it was found that in birds' liver and eggs the PCB residues were greater than the organochlorine pesticide residues. PCB's have also been found in fish, mussels and birds from the River Rhine and the Netherlands costal areas[7], in marine animals in Sweden, England and the U.S.A.[7,8] and in other wildlife samples[6,9-11]. Polychlorinated biphenyls have been found in human adipose tissue[12], samples of human milk[13] and in foods (margarine, vegetable oils and particularly fish)[14].

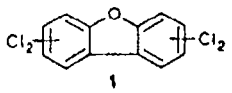
Essentially, the same type of residue pattern is becoming apparent for the polychlorinated biphenyls that has been found for the persistent organochlorine insecticides. The PCB's are extremely stable; chemically, fat soluble and hence persistent in the environment.

Polychlorinated biphenyls and polychlorinated triphenyls have been found to be estrogenically active[15] — in a series of PCB's the compounds containing up to 48% chlorine were active. On a weight basis polychlorinated biphenyl preparations (Aroclor 1221) have been shown to have an estradiol-degrading potential about five times that of *p,p'*-DDE or technical grade DDT[5].

PCB's are inducers of hepatic enzymes and together with other chlorinated compounds may be responsible for aberrations in calcium metabolism in certain species of birds[5] and are generally considered to be more of a potent threat than DDT to our declining bird populations, especially for predatory birds that accumulate fairly high levels of PCB's.

Hydropericardium, occasionally accompanied by abdominal edema was

found in chicks[16-18] and Japanese quail[7] after ingestion of PCB of American (Aroclor) and French (Phenoclor) origin respectively. The occurrence of lesions resembling those of chick-edema in birds fed PCB[18,19] has also been reported. In most recent work, Vos *et al.*[20] described the identification and toxicological evaluation of chlorinated dibenzofuran and chlorinated naphthalene in two commercial polychlorinated biphenyls. A combination of toxicological, pathological and chemical-analytical data (including mass spectroscopy) strongly suggested the identity of tetra- and pentachlorodibenzofurans (1 and 2, respectively) as toxic factors in the PCB's Clophen A-60 and Phenoclor DP6.



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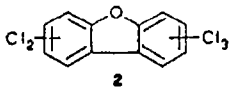
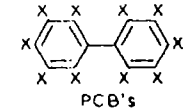


2

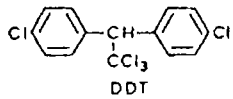
The occurrence of dibenzofuran derivatives was suggested via a consideration of the manufacture of PCB's and particularly in the procedure for the distillation of crude PCB in which sodium hydroxide can be used[21]. PCB can react with sodium hydroxide at elevated temperatures to yield phenolic compounds and can for example yield polychlorohydroxybiphenyls via saponification by sodium hydroxide in a polyhydric alcohol medium[22], subsequent loss of hydrochloric acid could then produce chlorinated dibenzofuran derivatives.

The biological interactions of polychlorinated biphenyls and insecticides was reported by Lichtenstein *et al.* [23] who showed that many of the PCB's were toxic to *Drosophila melanogaster* Meigen and houseflies *Musca domestica* L. (but to a lesser extent than dieldrin or DDT: their toxicity increased with a decrease in their chlorine contents). Moreover, sublethal dosages of several of the plasticizer PCB's increased the toxicity of dieldrin and DDT.

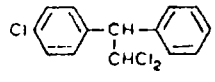
Although PCB's are not pesticides *per se*, they are included in about three dozen pesticide products registered by the USDA[24]. Because of their similarity in structure and chemical properties, PCB's, if present in a sample, are carried through the usual pesticide extraction and screening procedures and are frequently mistaken for DDT in monitoring tests.



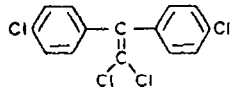
PCB's



DDT



DDD



DDE

Phthalate ester plasticizers. Phthalate esters are among the most widely used compounds as plasticizers in a variety of lacquers, varnishes, paints, co-polymers and plastics.

In general, phthalate esters have been reported to have a lower order of toxicity for experimental animals[25,26] and thus have been approved for use in packaging materials for food intended for human consumption. However, Guess and coworkers[27-30] have demonstrated the subtle toxicities (tissue culture cell death or enhanced growth, changes in antibody reactivity and irritation as evidenced by dye extravasation) of plasticizers and stabilizers used in the manufacture of polyvinyl plastics.

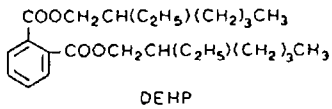
Citrate and phthalate ester plasticizers such as bis (2-ethylhexyl)phthalate and acetylated tri-butyl citrate were found to be leached from plasticized polyvinyl chloride (PVC)[31]. The significance of exposure time on the leaching of these plasticizers from PVC is important since the plastic is commonly used in in-dwelling surgical devices, *e.g.* catheters, and in pharmaceutical containers. Calley *et al.*[30] described the toxicology of a series of phthalate esters.

It has been previously shown that certain plastic devices used medically can release one or more ingredients into tissue or solvent systems[32-34].

The four citric acid esters used as plasticizers (*e.g.* triethyl, acetyl triethyl-tributyl- and acetyl tributyl citrate) have well defined and marked pharmacological activity when administered parenterally (all four have local anesthetic action and can block neural transmission when they come in direct contact with a nerve trunk, and also stimulate the nerve trunk)[30].

Phthalate ester plasticizers were found to be extracted by blood from plastic tubing and from plastic bags used for blood storage. Butylglycolbutyl phthalate (BGBP) was found to be metabolized by isolated perfused rat liver to glycolyl phthalate. A second phthalate ester plasticizer di(2-ethylhexyl)phthalate (DEHP) which is commonly used in plastics in biological and medical practice was found accumulated in the liver unchanged. In addition, it was identified in samples of human tissue (spleen, liver, lung and abdominal fat) taken from patients who had received transfusions of blood stored in plastic bags[35].

BGBP Glycolyl phthalate



DEHP

The isolation of plasticizers such as DEHP from the anticoagulant citric acid-dextrose solutions stored in disposable polyvinyl chloride blood bag assemblies has also been documented[36,37].

In addition to evidence of phthalate ester plasticizers in certain foodstuffs such as milk[38], there has been evidence concerning the presence of these plasticizers in animal tissues such as beef pineal gland[39] and heart[40].

The teratogenic effects in the chick embryo caused by esters of phthalic acid was described by Bower *et al.*[41]. Dibutoxyethyl phthalate caused teratogenesis in the

developing chick embryo and also di-2-methoxyethyl- and octa-isodecyl phthalate were capable of causing damage to the central nervous system of the developing chick embryo. Toxigenic effects in different mammals caused by several esters of phthalic acid have been well documented[29,42-45].

The effect of chemical sterilization of plastic items and their contents with primarily alkylating agents such as ethylene- and propylene oxide adds yet another dimension to the toxicities and potential hazards that might occur. This is especially true in the interaction of these gas sterilization agents with rubber and polyvinyl components of many devices. For example, the ethylene oxide reaction product [2-(2-hydroxyethyl-mercapto)benzothiazole] of the vulcanization accelerator 2-mercaptobenzothiazole was found to be more toxic than the precursor using cells in culture mice and rabbits[46]. O'Leary and Guess[47] demonstrated the homolyzing ability of known amounts of ethylene oxide to that of freshly gas-sterilized plastic pharmaceutical products as well as the effects of ester type plastics upon the sorption of ethylene oxide into polyvinyl chloride products.

Organo tin compounds. Organo tins are compounds which contain at least one tin-carbon bond and if all radicals attached to tin through carbon are designated R, and all other substituents X, the following series are obtained: R_4Sn, R_3SnX, R_2SnX_2 and $RSnX_3$. (R may be simple aliphatic or aromatic hydrocarbon radicals and X halide, hydroxide, OR, SH, SR or acyl radicals). Most of the organo tins of industrial and pesticidal utility are the derivatives of quadrivalent tin.

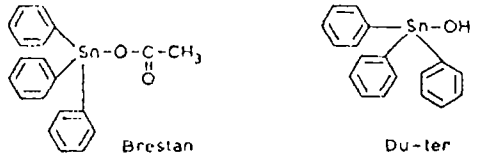
Organo tin compounds are used in plastics and polymers as stabilizers of vinyl resins and oxygen-containing polymers and polyamides against degradation by heat and/or u.v. light; to control pore structure in polyurethane films; preserve the transparency of polyvinyl chloride. Compounds used for this purpose are of the type R_2SnX (*e.g.* dioctyl tin and dibutyl tin dilaurates, maleates, oxides, etc.), and are generally present to the extent of 1-2% of the finished polymer.

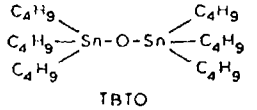
The increased use of PVC in the food packaging and disposable medical articles fields has focused the need to elicit both the amount, and nature, of tin stabilizer residues. Organo tin compounds used to stabilize poly (vinyl chloride) during container-forming operations can migrate into foodstuffs packaged in such containers. The FDA permits the presence in certain foodstuffs, as a result of such migration of two organo tin compounds, namely di-octyl SS-b (iso-octylmercaptoacetate) and di-octyl tin maleate polymer. The concentration of either, or any combination of both, may not exceed 1 p.p.m. which represents 0.158 or 0.259 p.p.m. of tin (as organo tin), respectively, in the foodstuff.

Organo tins are employed in a host of other applications that include: (*a*) In rubber products and paints: as antioxidants and anticracking agents; to retard rubber deteriorations and as stabilizers of chlorinated rubbers or chlorinated paints; (*b*) In transformers, capacitors and cables: to prevent corrosion by serving as scavengers for HCl formed if a short circuit occurred in transformers, etc., using pyranols or chlorinated diphenyls (tetraphenyl tin is usefully employed for this purpose); (*c*) In lubricants and textile oils: as acute oxidants and corrosion-reducing adjuvants for lubricants; as anti-oxidants for textile oils; (*d*) As activators and catalysts: in oxida-

tion, polymerization (polyesters and silicone elastomers) as Ziegler-Natta type catalysts for polymerization of olefins; (*e*) Tin-containing polymers: numerous tin-containing polymers and macromolecules have been prepared with tin in the main chain or as substituent as well as tin analogs of silicons (in which carbon and tin alternate); (*f*) Miscellaneous uses of organo tins include: treatment of fibreglass with alkyl and aryl tin compounds for adhesion to resins; curing catalysts for application of silicons to textiles, paper.

The biocidal applications of organo tin include: (*a*) agricultural fungicides: triphenyl tin acetate (Brestan; fentin acetate) and triphenyl tin hydroxide (Du-ter; fentin hydroxide) and bis(tri-n-butyl tin) oxide (TBTO);





TBTO

(*b*) General fungicidal action (*e.g.* triphenyl tin chloride): in paints, preservation of manila and sisal ropes, leather, textiles, to confer mildew resistance to fabrics, for protection of jute and jute bags; wood preservative, slimicide; paper production process paper; (*c*) Bactericides and biostats: disinfectant (triantyl tin), bactericides for seeds; (*d*) Anthelmintics: against worms in poultry (dibutyl tin laurate, tin oleate, tetraisobutyl tin); (*e*) Nematocide: *p*-bromophenoxy triethyl tin; (*f*) Herbicides: vinyl tin compounds (trivinyl tin chloride); (*g*) Rodent repellants: protecting food in treated bags (tributyl tin chloride, triphenyl tin chloride and acetate); (*h*) Molluscides: triphenyl tins; (*i*) Ovicides: trialkyl and triaryl tin chlorides (*e.g.* R_3SnCl, R being methyl, ethyl or propyl) as insecticides and ovicides in combination with DDT or pyrethrum.

The mode of action of organo tins in mammals can be delineated as the degree of alkylation of the tin compound *per se*. In general, in the whole animal, pharmacological and toxicological effects of trialkyl tins are confined to the nervous system[48,49]. For rats, the oral toxicities[50] of the trialkyl tins are in the order: triethyl > trimethyl > triisopropyl > tri-n-butyl. (The decrease of toxicity with increasing length of alkyl chain is analogous to that observed with di- and tetraalkyl tins).

The conversion of tetraalkyl tins to trialkyl tins[51–53] *in vivo* (as demonstrated for tetraethyl tin) accounts for the latent toxicity of the tetraalkyl tins, with the site of the conversion being the liver[48,53]. From the toxicological point of view, the tetraalkyl tins can thus be considered to behave in a manner analogous to their trialkyl tin counterparts[54]. (This conversion of a tetraalkyl to a trialkyl metal has also been shown for tetraethyl lead[48,55,56], and may be a general phenomena). Once tetraethyl tin

has been converted to triethyl tin, it appears to persist in the body in that form without apparent further reaction to the dialkyl derivative. The trialkyl tin ion is a stable entity which is toxic *per se* and persists for some time in the tissues[52]. Long-term feeding experiments with triethyl tin have disclosed some testicular atrophy in addition to lesions confined to the central nervous system[49].

Triethyl tins and diethyl tins ionize in aqueous solution[57,58] with production of the univalent $(C_2H_5)Sn^+$ and divalent $(C_2H_5)_2Sn^{++}$ cations, respectively. It is reasonable to assume that trialkyl and triaryl tins exert their biological action as R_3Sn^+ ions or as the undissociated hydroxide R_3SnOH formed on dissociation.

The dealkylation of diethyl tin by the rat has been reported[59], with diethylation occurring in both the gut and tissues. The induction of biliary and hepatic lesions by dibutyl tin salts in rats has also been described[60].

Triphenyl tins, $(C_6H_5)_3SnX$, (where X was halide, hydroxide, alkyl or alkenyl, aryl or alicyclic radicals and ester groups or organic acids) have been found to be chemosterilants[61,62] when fed to adult houseflies.

Many of the triphenyl tins were found to be superior as chemosterilants, to the aziridines, if both groups were administered orally. The highest chemosterilizing activity was shown by triphenyl tins in which X is mobile and the triphenyl ion is obtained, *e.g.* halides, hydroxide, sulphide, alkenyl and ester derivatives (but not phenyl or butyl).

Triphenyl tins are mainly used in agriculture as fungicides (*e.g.* Brestan, TBTO). In the finely-divided state in which triphenyl tins are applied to plants, they are susceptible to light and oxygen[63].

Phenyl groups are gradually split off with step-by-step loss in toxicity. Triphenyl tins decompose slowly into diphenyl tins and the final stage of non-toxic inorganic quadrivalent tin compounds is probably reached through the unstable intermediate monophenyl tins[64], *viz.*,

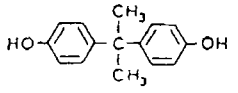
$$(C_6H_5)_3Sn- \longrightarrow (C_6H_5)_2Sn\!\!\left\langle \right. \longrightarrow [C_6H_5Sn\!\!\left\langle \right.] \longrightarrow -\underset{|}{\overset{|}{Sn}}-$$

Pate and Hays[65] described several degenerative changes in testicular tissue of male albino rats treated with triphenyl tin acetate and chloride. Complete sterility was achieved after 19 days of treatment following oral administration of triphenyl tin acetate, a decrease in the number of cell layers per seminiferous tubule, a decrease in tubule diameter and overall testicular size, a depletion of the more advanced cell forms from the tubules and a closing of tubule lumina.

Tricyclohexyl tin hydroxide is used as a miticide (Plictran, miticide) for apples, pears and citrus fruits. Exposure of tricyclohexyl tin hydroxide to u.v. light has indicated that the compound degrades to cyclohexyl tin and inorganic tin[66].

Also, it has been found that when fruit is harvested at varying periods after the final spray treatment, the ratio of tricyclohexyl tin to total tin decreases with time. Residue half-lives for tricyclohexyl tin hydroxide in apples and pears were: 5–6 weeks for the apples and 2 weeks for pears following application of Plictran (0.84–1.00 ppm for apples and 0.40–0.99 ppm for pears).

Bisphenol. Bisphenol A[(2.2-bis(*p*-hydroxyphenyl) propane] as a copolymer is an important monomer in several resins used as food packaging materials for industrial processing and consumer use.



Bisphenol A

The metabolic fate and properties of bisphenol A are of importance since some unreacted monomer does migrate to food. The metabolism of bisphenol A in the rat following oral administration[67] indicates that less than 1% of the material present in urine was free bisphenol A while the feces contained 35% free bisphenol A and an additional 35% was identified as a hydroxylated product of bisphenol A.

It is important to also note the marked extrogenic activity of bisphenol A[15] (the minimum effective subcutaneous dose was 0.25 mg in the sensitive 18h-glycogen response of the rat uterus).

Rubber additives

More than 600 different compounds are employed in rubber technology. Generically, however, the organic additives could be grouped into a dozen or so chemical classifications. Among these are the thiurams, dithiocarbamates, thiazoles, sulfenamides, thioureas, guanidines, amines, amides, quinolines and phenols. The categories of utility include accelerators, activators, antioxidants, blowing agents, vulcanizers, retarders, reinforcing agents, plasticizers, dusting or dipping agents and inert fillers. Table I illustrates the structures of a number of classes of common rubber additives. It is of interest to note that ethyl selenac (selenium diethyldithiocarbamate) which is used both as rubber accelerator and fungicide is carcinogenic in the mouse[68], while the rubber additive polymerized *N*-nitroso-2,2,4-trimethyl-1,2-dihydroquinoline has recently been found carcinogenic in the rat[69,70].

The dithiocarbamates and their metal salts have also wide utility as fungicides and their decomposition products include: alkyl thiourea, ethylene thiuram monosulfide, carbon disulfide, carbonyl sulfide, hydrogen sulfide, metal sulfide salts and elemental sulfur. Both thiuram[71] and thiourea are carcinogenic for the thyroid[72], and 4,4′-methylene bis (2-methylaniline) and 4,4′-methylene bis (2-chloroaniline) are liver and lung carcinogens in the rat[73].

Brightening agents

Optical brighteners or optical bleaches were first introduced into household products about 23 years ago as detergent additives. These compounds were *generally* used at levels varying from a few hundredths of 1% to a maximum of 0.2% in such products but today's quality detergents contain optical brighteners, often at levels higher than 0.5%. They are deposited in minute amounts on fabrics during laundering and emit a bluish fluorescence when exposed to ultraviolet radiation, thus improving the appearance of whiteness or brighteners in the fabrics.

TABLE I

COMMON RUBBER ADDITIVES

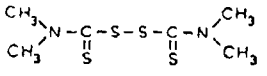
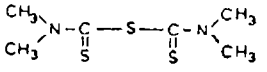
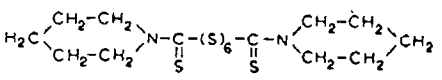
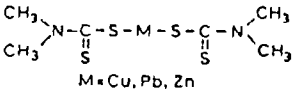
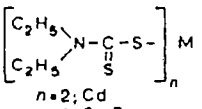
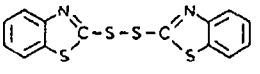
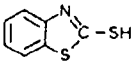
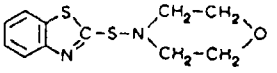
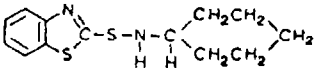
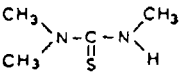
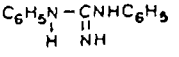
Category	*Structure*
Accelerators	
Tetramethylthiuram disulfide	
Tetramethylthiuram monosulfide	
Dipentamethylenethiuram hexasulfide	
Metallodimethyl- and diethyldithiocarbamates	 M = Cu, Pb, Zn  n = 2; Cd n = 4; Se, Te
Benzothiazyl disulfide	
2-Mercaptobenzothiazole	
N-Oxydiethylenebenzothiazole-2-sulfenamide	
N-Cyclohexyl-2-benzothiazolesulfenamide	
Trimethyl thiourea	
Diphenyl guanidine	

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TABLE I (continued)

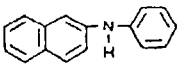
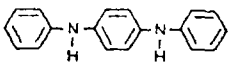
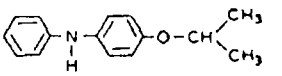
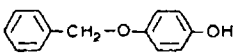
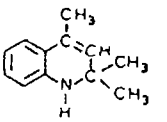
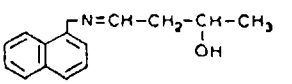
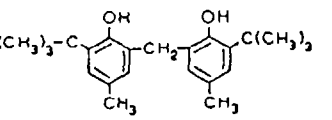
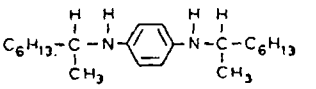
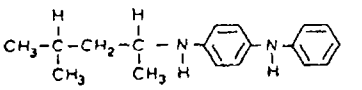
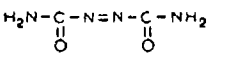
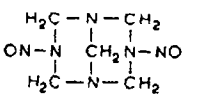
Category	*Structure*
Antioxidants Phenyl-β-naphthylamine	
Diphenyl-*p*-phenylenediamine	
p-Isopropoxy diphenylamine	
Hydroquinone monobenzyl ether	
1,2-Dihydro-2,2,4-trimethyl quinoline	
Aldol-α-naphthylamine	
2,2-Methylene-bis-(4-methyl-6-*tert*-butyl phenol)	
Anti-ozonants *N,N'*-Di(2-octyl)-*p*-phenylene diamine	
N-(1,3-Dimethylbutyl)-*N'*-phenyl-*p*-phenylene-diamine	
Blowing agents Azodicarbonamide	
Dinitrosopentamethylene tetramine (3,7-Dinitroso-1,3,5,7-tetraazabicyclo[3,3,1]-nonane)	

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TABLE I (continued)

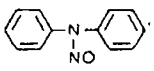
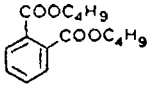
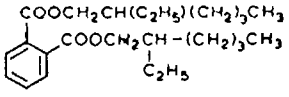
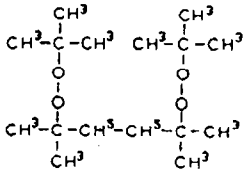
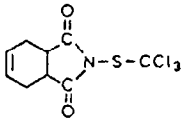
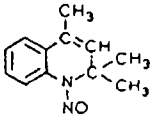
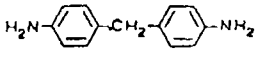
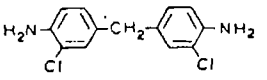
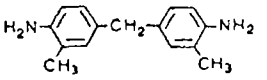
Category	*Structure*
Retarders	
N-Nitrosodiphenylamine	
Salicylic acid	
Plasticizers	
Dibutylphthalate	
Dioctylphthalate [bis(2-ethylhexyl)phthalate]	
Vulcanizing agents	
2,5-Bis(*tert*-butyl peroxy)-2,5-dimethyl hexane	
Fungicides	
N-Trichloromethylthio-4-cyclohexene-1,2-dicarboximide (Captan)	
Miscellaneous additives	
Polymerized *N*-nitroso-2,2,4-trimethyl-1,2-dihydroquinoline	
4,4-Diaminodiphenylmethane	

TABLE I (continued)

Category	*Structure*
4,4'-Methylene bis-(2-chloroaniline)	
4,4'-Methylene bis-(2-methylaniline)	

The most commonly used cotton brighteners, shown in Fig. 1A are bis triazinyl derivatives of 4,4'-diaminostilbene-2,2'-disulfonic acid. These so-called CC/DAS brighteners are prepared from 2 moles of cyanuric chloride (CC) and 1 mole of the disodium salt of diaminostilbene disulfonic acid (DAS). With the exception of brightener DMDDEA all are reaction products of 1 mole of CC/DAS with 2 moles of aniline. Brightener DMDDEA is the reaction product of 1 mole of CC/DAS and 2 moles of sulfanilic or metanillic acid.

A number of typical structures of brighteners that are stable to chlorine bleach in the wash liquor are shown in Fig. 1B. These are benzidine sulfone disulfonic acid (brightener BS), naphthotriazoylstilbene sulfonic acid (brightener NTS, R = H) and benzimidazolyl (brightener BBI) derivatives.

The general structures of typical nylon and wool brighteners are shown in Fig. 1C and include the derivatives of amino coumarin (brightener AC) and diphenylpyrazoline (brightener DP), none of which are stable to chlorine bleach. The general structures of polyester brighteners that also have affinity for polyamide fibers are shown in Fig. 1D and include bisbenzoxazolyl (brightener BBO), naphthoxazolyl (brightener NOS) and naphthotriazolyl (brightener NTSA) derivatives.

The (CC/DAS) brighteners behave like direct, dyestuffs on cotton[74] Brightening of hydrophobic fibers such as nylon, polyester and acetate in an alkaline detergent liquor takes place by a procedure similar to the dyeing of these fibers by dispersed dyestuffs[74].

Although the solubility of the commonly used brighteners in a detergent wash liquor is relatively low, it is still high enough to allow a sufficient amount to dissolve. The exhaust of brightener onto the fiber and migration into the fiber allow more brightener to dissolve in the liquor. It is claimed that the total concentration of brightener in the liquor of the modern American home laundry would be only 3–10 mg/liter, even if all the brightener were in solution at one time[75]. Of all laundering aids commonly added to the wash liquor apparently only active chlorine products affect the stability of some brighteners. The extent of attack on the so-called bleach unstable brighteners depends on their chemical structure, temperature, amount of bleach used, etc.

Differences in stability to hypochlorite and dichloroisocyanurate bleaches

exist also among the CC/DAS brighteners. This would appear to indicate that the bleach stability of these compounds is directly or indirectly related to the amine which is used for the reaction with the second reactive chlorine on the triazine ring.

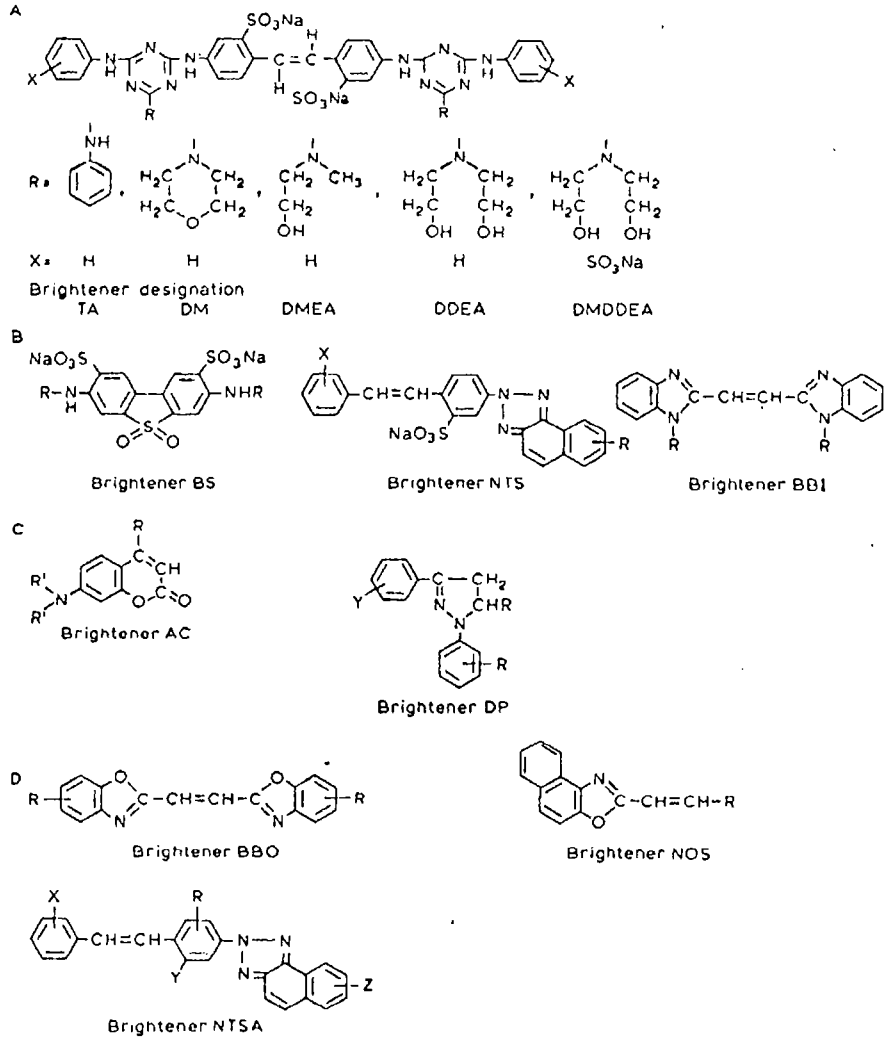
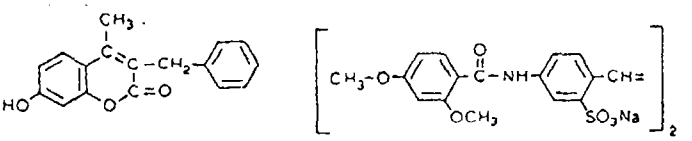


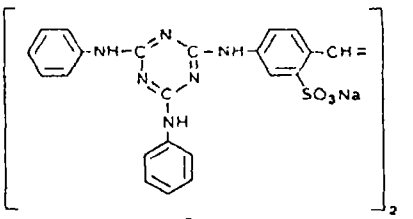
Fig. 1. Structures of optical brighteners. A, Bis triazinyl derivatives of 4,4′-diaminostilbene-2,2′-disulfonic acid (CC/DAS cotton brighteners). B, Bleach-stable brighteners. C, Nylon and wool brighteners. D, Polyester and polyamide brighteners.

The combined action of optical brighteners and ultraviolet light in the production of tumors has been reported by Bingham and Falk[76].

The optical brighteners studied were: 3-benzyl-4-methyl-7-hydroxy coumarin (3), disodium-4,4′-bis (2,4-dimethoxybenzamido)-2,2′-stilbenedisulfonate (4), disodium-4,4′-bis (4,6-dianilino-*S*-triazin-2-yl)-amino-2,2′-stilbenedisulfonate (5).



3 4



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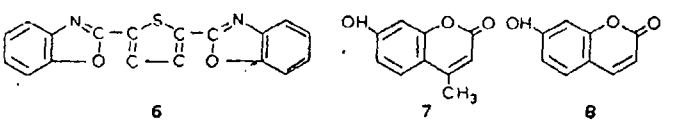
Tumors were not found in any mice receiving topical application of the optical brightener in DMSO alone, but with addition of ultraviolet light (6 h/day on 5 days/week to a germicidal lamp having 60% of its energy at 254 mμ) a high incidence of tumors developed that resembled grossly the tumors (squamous cell carcinomas) arising from repeated application of carcinogenic polycyclid aromatic hydrocarbons.

Since the use of optical brighteners is widespread in laundry products such as detergents, starches, fabric softeners, in fabrics and paper and in miscellaneous products such as toilet soap and all-purpose cleaners, questions relating to the potential hazard of dermal contact and/or penetration of the above brighteners as well as those listed in Fig. 1 A-D, are germane.

Also of importance is the recent finding[77] that the optical brightening agent (6) has been recovered from fish in Sweden suggesting a potential hazard of wash liquors containing other optical brighteners being concentrated in marine organisms and fish and hence available for human consumption.

Another interesting brightening agent is 4-methyl umbelliferone (7-hydroxy--4-methyl coumarin) (7) that is used as a whitener in laundry detergents as well as



6 7 8

a brightener in dentrifrices. It is related to umbelliferone (7-hydroxy coumarin) (8) which is used in sunscreen lotions and creams. Both coumarin derivatives had been shown to induce chromosome breakage in *allium cepa*[78,79].

Miscellaneous agents

Trichloroethylene and tetrachloroethylene. Both trichloroethylene and tetrachloroethylene (perchloroethylene) are used extensively as industrial solvents (primarily for drycleaning and degreasing), the latter has been finding increasing use since the advent of coin-operated drycleaning. Trichloroethylene is also used with other chemicals such as polymerized resins of phenol-formaldehyde, urea-formal-

dehyde and epoxides in the production of special fiber glasses. Tetrachloroethylene is used in small amounts as a commodity fumigant. Both trichloro- and tetrachloroethylene have been shown to be neurotoxic[80-83], but tetrachloroethylene is believed to be more hepatoxic than the trichloro derivative.

The metabolism of ^{36}C-labeled trichloro- and tetrachloroethylene was studied by Daniel[84] who found that both compounds are largely excreted through the lungs. It is well known that trichloroethylene is excreted in the urine as trichloroacetic acid and trichloroethanol in all species of experimental animals studies. In addition to these compounds, monochloroacetic acid is also a urinary metabolite of man.

A point of major importance is the nature of the rearrangement which results in the formation of 2,2,2-trichloroethanol and trichloroacetic acid from 1,1,2-trichloroethylene. This has been shown to be an intra-molecular rearrangement of trichloroethylene and no exchange of chloride with the body chloride pool. Fig. 2 illustrates the metabolic pathways of trichloroethylene and tetrachloroethylene.

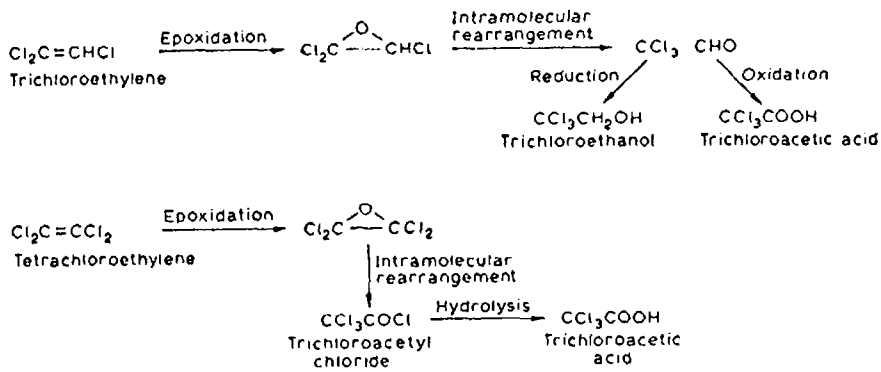


Fig. 2. Metabolic pathways of trichloroethylene and tetrachloroethylene in the rat.

The formation of the intermediate oxide was postulated by Powell[85]. Trichloroethylene oxide is believed to be formed *in vitro* when trichloroethylene is oxygenated in the presence of actinic radiation. Rearrangement of the oxide yields trichloroacetaldehyde (chloral). The formation of chloral in men exposed to trichloroethylene vapor has been reported[86]. Chloral appeared in the blood within 30 min of exposure but subsequently underwent rapid metabolism. The oxidation of chloral to trichloro acetic acid is reported to be carried out by an enzyme present in the liver of a variety of experimental animals[87].

The reduction of chloral to trichloroethanol would involve alcohol dehydrogenase. The metabolism of tetrachloroethylene may also involve the intermediate oxidation formation. For example, following exposure of tetrachloroethylene vapor for 2 h in mice, the urinary metabolites included 52% trichloroacetic acid, 11% oxalic acid and traces of dichloroacetic acid. An epoxide intermediate was postulated to account for these products[88] as shown in Fig. 2.

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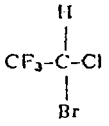
The acid chloride would be rapidly hydrolyzed to trichloroacetic acid and neither trichloroethanol or oxalic acid would be formed.

In all of the above discussion of the metabolism of trichloro- and tetrachloroethylene it is important to note the mutagenicity of the intermediate chloral hydrate[89,90] as well as the potential mutagenicity and carcinogenicity of epoxides in general with specific reference to tetrachloroethylene oxide postulated above.

It is of added importance to consider the similarity of types of metabolic products (to those discussed above) of the important anesthetics halothane (1,1,1-trifluoro-2-bromo-2-chloroethane) (**9**) and fluoroxene (2,2,2-trifluoroethyl vinyl ether) (**10**).



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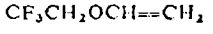

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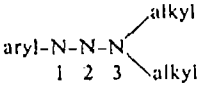
Trifluoroethanol, trifluoroacetaldehyde hydrate and trifluoroacetic acid are the metabolites of both anesthetics and their formation may proceed via an intermediate epoxidation and intramolecular rearrangement as described for trichloro- and tetrachloroethylene in Fig. 2. Little is known of the chronic toxicities of the above fluoro-metabolites.

Triazenes. Certain triazenes have technical importance as intermediates in the "Rapidogen" dyeing process[91] and aryl dialkyl triazenes have been patented for use as rodent repellants and herbicides[91–94]. Other triazenes have been evaluated as carcinostatic agents[95–98].

1-Phenyl-3,3-dimethyltriazene is both a potent carcinogen[99] and teratogen in rats[100,101]. Certain other 1-aryl-3,3-dialkyl triazenes of the general formula:



are also potent nemotropic carcinogens in rats[102]. The potency increases in the order: phenyl, 3-pyridyl, pyridyl-*N*-oxide, and methyl and ethyl, respectively.

In acid medium, aryldialkyltriazenes are hydrolyzed to yield aryl diazonium salts and a secondary amine. (It is of importance to note that methyl phenylnitrosamine and phenylnitrosourea are both carcinogenic[103,104] forming probably phenyldiazoniumion as a reactive intermediate.)

Preussmann *et al.*[105] studied the enzymatic dealkylation by rat liver and lung microsomal fraction *in vitro*. 1-Phenyl-3,3-dimethyl triazene was found to be oxidatively dealkylated to form the corresponding aldehyde (formaldehyde) and aniline was also shown to be a metabolite. The results suggest that carcinogenic aryl dialkyl triazenes are dealkylated to form aryl-mono alkyl triazenes as proximate carcinogens. Aryl mono-alkyl triazenes are known alkylating agents and the carcinogenic activity of triazenes was explained by alkylation of biopolymers (nucleic acids). Fig. 3 illustrates a proposed activation mechanism of carcinogenic phenyl dimethyl triazene

to form phenyl monomethyl triazene as proximate carcinogen and carbonium ion as ultimate alkylating agent. The proposed reaction mechanism, however, does not exclude that certain triazenes may act by a purely chemical heterolysis to form aryl diazonium ions as reactive intermediates (for example, the very local sarcomas after subcutaneous injection of 1-phenyl-3,3-dimethyl triazene may be explained on this basis).

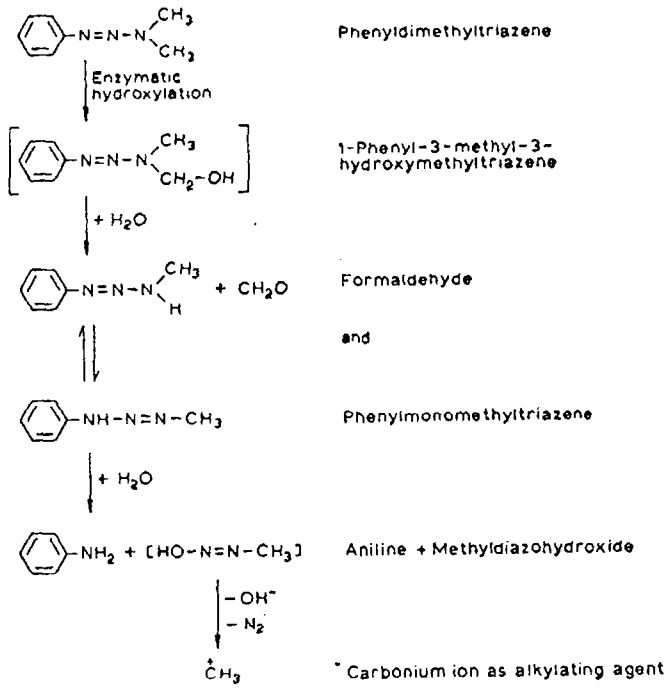
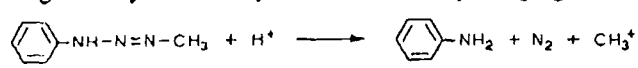


Fig. 3. Proposed activation mechanism of carcinogenic phenyldimethyltriazene to form phenylmonomethyltriazene as proximate carcinogen, and carbonium ion as ultimate alkylating agent[102].

The *in vitro* alkylation of guanosine, RNA and DNA with aryl-monoalkyltriazenes to form 7-alkylguanine was demonstrated by Preussmann and von Hodenberg[106]. Aryl monoalkyltriazenes are alkylating agents[107–110] as shown:



The alkylation of biopolymers was earlier proposed as the first step in carcinogenesis by aryldialkyltriazenes[105]. Reactions of 1-phenyl-3-monomethyl- and monoethyl triazenes, respectively, with guanosine, RNA and DNA resulted in the formation of 7-methyl and 7-ethyl guanine.

It is germane to consider the closely related carcinogenic alkylating substances consisting of: *N*-nitroso, hydrazo-, azo-, and azoxyalkanes since, as we have discussed previously, many environmental agents either possess the above moieties or are transformed via metabolic and/or degradative pathways to them.

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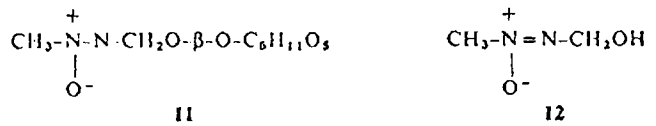
The first and decisive step in the activation of these groups in an enzymatic α-C-hydroxylation of an alkyl residue, which is then cleaved off as the corresponding aldehyde (an alkyl diazohydroxide or an alkyl diazonium ion is probably formed as an alkylating intermediate). The naturally occurring azoxyalkane cycasin (methylazoxymethanol glucuride) (**11**) is transformed to its methylazoxymethanol (**12**).



11 **12**

This proximate carcinogen is then easily hydrolyzed to formaldehyde and an alkylating agent, probably methyl diimine oxide, which is a tautomer of methyldiazohydroxide.

Azoalkanes could possibly be oxidized *in vivo* to yield azoxyalkanes. Dealkylation of alkanes could form alkyl diimines which could possess alkylating activity. Fig. 4 illustrates the proposed reaction mechanism of hydrazo-, azo- and azoxyalkanes according to Preussmann *et al.*[111].

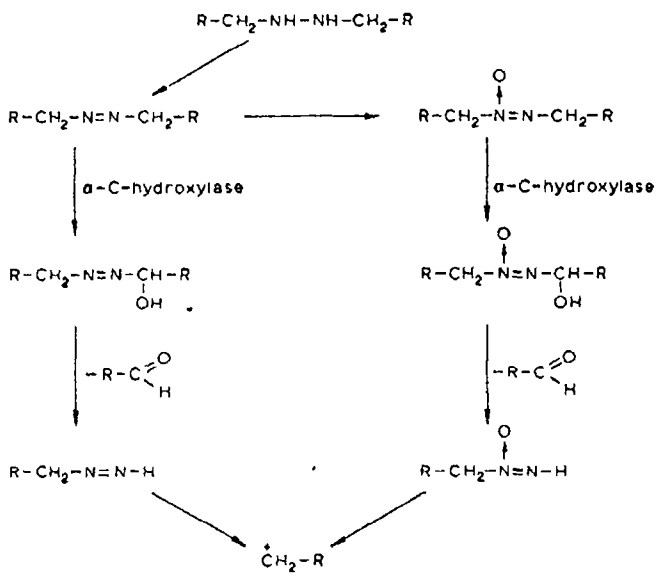


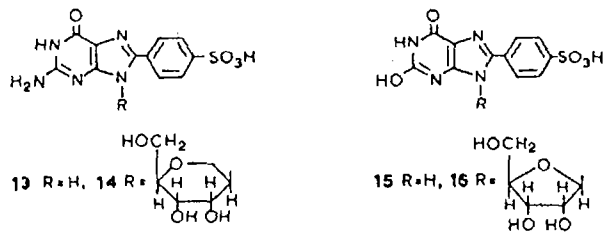
Fig. 4. Proposed reaction mechanism of hydrazo-, azo- and azoxyalkanes.

The alkylation of nucleic acids, particularly at N-7 in guanine, and the resulting change of the genetic code in cells is considered as the initiation of their carcinogenic transformation.

Since the "active forms" in all three groups of substances (*viz.*, (*a*) nitroso compounds, (*b*) hydrazo, azo, and azoxyalkanes, and (*c*) 1-aryl-3,3-dialkyl triazenes) are the same, *e.g.* alkyldiazonium compounds, the specificity of the effects must most probably be attributed to the whole molecule of the "transport forms" or to their

enzymatic activation. The detection of carcinogenic properties in diazomethane and diazoacetate as well as in directly acting alkylating agents such as alkyl halides, aziridines, dialkyl sulfates and 1,3-propane sulfone gives considerable support to the alkylation theory[102].

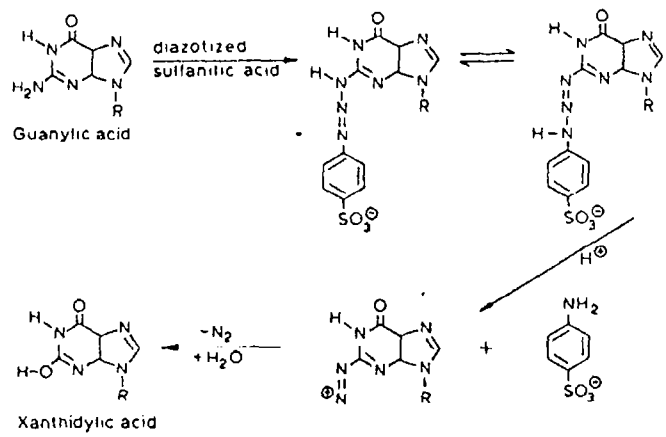
A number of reported reactions of mono-nucleic acids with diazonium salts *in vitro* are informative[112-114]. For example, the arylation of guanine in the 8-position by diazonium salts has been demonstrated[115].



Typical compounds formed include δ-*p*-benzolsulfoguanine (13).

Guanine reacts with diazonium salts to yield guanine δ-azo compounds which can further reduce to δ-amino guanine and arylamine[113,116] while adenine does not undergo the analogous reaction.

Kössel[112] described the reaction of mononucleotides with diazonium salts to proceed as shown:



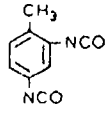
The mononucleotides guanyl-, adenyl and cytidylic acid react with diazotized sulfanilic acid at pH 10–11 forming colored dyes (pigments) which absorb strongly at 370–440 mμ. Guanylic acid reacts more rapidly than adenylic or cytidylic acid while uridyl- and thymidylic acids show no reacion with diazonium salts. At pH 3 all the pigments decompose again to the starting materials. The pigment formation is inhibited in the presence of formaldehyde. The reaction products are suggested to be diazoamino compounds.

Reactions of diazonium salts with nucleic acids were investigated by Pochon and Michelson[117]. Diazonium salts obtained from 2-amino-*p*-benzene disulphonic acid and 2-aminonaphthalene-1,5-disulphonic acid were found to be highly specific giving 8-substituted guanine residues. This type of reagent has been employed to mark DNA for studies by electron microscopy[118].

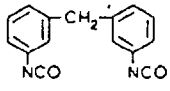
Polyphenyls. Certain polyphenyl compounds have been used as moderator coolants in nuclear reactors for some years and their toxicity is of importance should they be accidentally released. The chronic toxicity of polyphenyl mixtures have been reported[119,120]. At a daily dietary intake of 350 mg/kg or more Santowax OM, a mixture of terphenyls used as a coolant, causes severe and to some extent irreversible chemical nephrosis and interstitial nephritis in rats following prolonged ingestion. Santowax OM consists of a mixture of biphenyl (4.7%), *o*-terphenyl (64.1%), *m*-terphenyl (25.1%) and *p*-terphenyl (6.1%); while OMRE High Boilers consists of high boilers > 98%, biphenyl (< 0.1%), *o*-terphenyl (0.1%), *m*-terphenyl (< 0.1%, *p*-terphenyl (< 0.7) and inorganic (< 0.1%).

At a daily dietary intake of 33 mg/kg or more an OMRE High Boiler Sample (consisting of terphenyl and radiolytic and pyrolytic products derived thereof) induces a marked reticuloendothelial hyperplasia in rats following chronic oral administration, leading to an irreversible monolobular cirrhosis. The toxicity of the above reactor coolant to fish was described by Guthrie and Acres[121]. The acute toxicity in rabbits of polyphenyl compounds used as atomic reactor moderator coolants was described by Haley *et al.*[122]. *Ortho-* and *meta* terphenyls were the only polyphenyls that caused death after inhalation.

Diisocyanates and polyurethanes. The diisocyanates such as toluene-2,4-diisocyanate (TDI) and methylenediphenyldiisocyanate (MDI) are representative of chemically hghly reactive moieties that will combine with many organic compounds. The industrially useful reactions involve the combination with a resin, usually an organic polyhydric alcohol, to form a high molecular weight polymer of the polyurethane type. Polyurethanes are used as paints and varnishes, surface coatings, flexible and rigid foams, wire coverings and in thermal and sound insulation.



TDI



MDI

TDI is usually prepared from toluene-2,4-diamine and phosgene in a solvent such as *o*-dichlorobenzene or toluene. In the process where TDI is used on a very large scale in the manufacture of flexible foams, the highly exothermic reaction is controlled by the addition of appropriate catalysts (*e.g.* blowing agents such as azodicarbonamide). As a result of the exotherm, significant quantities of TDI vapor may appear in the atmosphere and in concentrations substantially above the present threshold limit value of 0.02 p.p.m.[123]. Prolonged exposure of workers to low air concentrations of TDI (0.1 p.p.m.) have been reported to produce a variety of acute and chronic respiratory effects[124–129].

Crude MDI used in rigid urethane foam formulations is prepared by treating the condensation product of aniline and formaldehyde with phosgene. Any uncondensed aniline initially present will be converted to phenyl isocyanate, which because of its volatility, is more toxic than the diisocyanates.

The hazards involved in the decomposition of polyurethanes have been suggested by Paisley[130]. For example the decomposition of polyurethanes used in wire insulation occurs at 220°C–275°C, producing iso-cyanates and *N*-oxides. (The temperature of a soldering iron in normal soldering operations is approximately 300°C.) The possibility of a serious incipient hazard in combatting fires involving buildings and refrigerated compartments, etc., where large quantities of polyurethane foams are used was also raised by Paisley[130].

The effects of physiologically active media on polyurethanes were studied by Lipatova and Verelovskii[131] to determine the potential use of polyurethanes as substitutes for tissues in surgery. The mechanical strength of polyurethanes were declined by 40–80% after a 5-month treatment in test solutions (*e.g.* physiological solution, gastric juice and pure HCl). The degradation of polyurethane in the model solution occurred as a result of cleavage of CO-bonds in the urethane group affording RNCOOH and R'OH. The degradation rate was inversely proportional to the number of intermolecular bonds in the polyurethane.

SUMMARY

We have examined but a small number of selected chemical agents from a spectra of environmental areas, *viz.*, drugs[1]; feed medicants and pesticides[2]; polymer and plastic ingredients, rubber additives, brightening agents and industrial chemicals with a view toward elaborating their potential hazard via a primary consideration of their structural analogies to known carcinogens, mutagens and/or teratogens. Efforts were made to cite where possible, the areas of primary environmental concern to man in terms of water, soil, air and food residues and attendant portals of entry of these agents as well as to stress their known biological and toxicological effects. Recognition was also made wherever feasible to the interrelationships and commonality of metabolites and degradation products from within the classes of compounds examined.

We stress the fact that not only are chemical pollutants (both synthetic and naturally occurring, as well as their metabolic and/or degradation products) capable of producing any one or more of a variety of acute and chronic toxicities, but they may also interact *in vitro* and *in vivo* to produce synergistic or potentiating effects.

Clearly the problem is staggering when one considers the myriad of new agents introduced into the environment annually on top of an already staggering number of present and potential hazards, but the time may also be short in eliciting the hazards of these agents to man.

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