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## CLEARINGHOUSE FINDS THREE CHEMICALS POSE RISK OF CANCER TO HUMANS; 38 MORE WILL GO ON TEST

The Clearinghouse on Environmental Carcinogens, established by NCI last year to deliver advice on a variety of issues encompassed by its name, has put its act together after a slow start and is now dispensing it in a big way.

The Clearinghouse is made up of nongovernment scientists, repre-

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*In Brief*

### CIGARETTE TAX WOULD RAISE $12 MILLION A YEAR FOR PENNSYLVANIA CANCER CONTROL, RESEARCH

PENNSYLVANIA CANCER Control & Research Act, to be funded by a one cent per pack cigarette tax, would provide $12 million a year in grants and contracts for research and control activities in the state. The bill authorizing the program "has better than 50% chance" of approval by the legislature, according to Samuel Fisher, Philadelphia CPA who is a member of the Governor's Task Force for Cancer Control. A separate bill will be required to levy the tax. The authorization bill says "the fund shall be used exclusively for grants and contracts to nonprofit Pennsylvania associations or governmental agencies for the purpose of cancer control and prevention, cancer education and training, cancer research. . . funded through grants and contracts." Fisher thinks this legislation might serve as a model for similar programs in other states and will send copies of the bill (House Bill 1120) to anyone writing to him at Samuel M. Fisher & Co., GSB Bldg Suite 800, City Line & Belmont Avenues, Philadelphia, Pa. 19131. . . . **"I DON'T AGREE** there should be a general retreat from paying the real indirect costs of research and to adopt a simple 10-15% formula, thus requiring institutions to bear the remainder of that burden," said President's Cancer Panel Chairman Benno Schmidt, responding to critics of the HEW formula that permits paying up to 75% of a grant for indirect costs. "The strength of this (cancer) program and others (supported by NIH) depends on the strength of institutions on which we rely. I'm not appalled at bearing a fair portion of indirect costs". . . . **PUBLICATIONS:** *Cancer Management,* by Walter Lawrence Jr. and Jose Terz of the Medical College of Virginia, "is written to provide guidelines and answers to the clinical management questions that are often raised by the general physician, the general surgeon, or the postgraduate trainee in the various specialties," according to the publisher, Grune & Stratton, 111 5th Ave., NYC 10003. Price, $38.50. . . . **"OF WHAT USE** Is Basic Medical Science? Of What Use Is A Baby?" is a convincing statement on basic medical science by Mahlon Hoagland, president and scientific director of the Worcester Foundation. Copies in pamphlet form may be obtained by writing to the Foundation, 222 Maple Ave., Shrewsbury, Mass. 01545.

## CLEARINGHOUSE FINDS TWO CHEMICALS NOT CARCINOGENS, TWO INCONCLUSIVE

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sentatives of the regulatory agencies, industry and consumer groups. It is charged with nominating chemicals for carcinogenicity testing, determining experimental designs for the conduct of tests, evaluating results from tests, and assessing human risk of chemicals found to be carcinogens.

The task of assessing human risk represented a new role for NCI. For the first time, with the advice of the Clearinghouse, NCI is taking an official position that certain chemicals do pose a carcinogenic threat to humans.

The Clearinghouse was first organized with a Data Evaluation Subgroup and a Risk Assessment Subgroup. They were merged after it became apparent their responsibilities overlapped. Before the merger, the Risk Assessment Subgroup determined that three chemicals were potential human carcinogens, two were not carcinogenic "under conditions of the test," and that tests were not adequate to determine if two others were carcinogens.

Chemicals which were determined as potentially carcinogenic to humans were:

**Tris (2,3-dibromopropyl) phosphate.** The Data Evaluation Subgroup had concluded that the bioassay of tris was adequate and that it was carcinogenic in both rats and mice. The Risk Assessment Subgroup discussed whether routes of exposure should be considered in making risk assessments. Sidney Wolfe, subgroup member and medical director of the Health Research Group, argued that it was the regulatory agencies' responsibility to determine risk for particular exposure routes based on their enabling legislation. In the case of tris, Wolfe said, exposure could be through skin absorption or ingestion by mouthing sleepware garments. Exposure might also occur in the workplace. Wolfe's motion that tris was a carcinogenic risk to humans was approved unanimously.

**Tetrachloroethylene.** This was one on which the two subgroups differed sharply. The Data Evaluation Subgroup had considered the rat study on the chemical unacceptable due to high early mortality—50% of males receiving the high dose died by week 44 and 50% of females by week 66. Median survival for controls was 88 weeks for males and 102 weeks for females. None of the early deaths was associated with tumors.

But in the mice study, a statistically significant increase in incidence of hepatocellular carcinomas was found in both males and females in the treated groups.

The Risk Assessment Subgroup discussed the significance to man of mouse liver tumors induced by chlorinated hydrocarbons. Arnold Brown, who is chairman of the subgroup as well as of the Clearinghouse, argued that the subgroup's recommendations must be based on the data at hand.

Clearinghouse member Verne Ray of Pfizer suggested that the hepatotoxicity of tetrachloroethylene obscured an interpretation of its carcinogenicity. He said that a statement on its carcinogenicity might be couched in terms that would consider the toxic effects. But Wolfe opposed a qualifying statement and pointed out that many known human carcinogens are highly toxic.

Wolfe's motion that tetrachloroethylene be considered a carcinogenic risk to humans was approved unanimously.

**Nitrilotriacetic acid (NTA).** Brown read from the report on NTA that it was shown to be carcinogenic to the urinary tracts of both rats and mice at the higher doses tested. Lower doses did not induce significant numbers of such lesions.

John Weisburger, of the American Health Foundation and a member of the Data Evaluation Subgroup, offered the opinion that NTA did not constitute a carcinogenic risk to man at the levels of its intended use. He said that its mechanism of action could be explained by the kidney damage at high dose levels. But Wolfe's motion that NTA was a carcinogenic risk to humans was accepted unanimously by the Risk Assessment Subgroup members.

The two chemicals for which the tests were inadequate:

**1,1,1-trichloroethane.** Liver tumors in the treated mice did not occur in statistically significant numbers when compared to the matched controls. Wolfe argued that they also should be evaluated against historical control animals. Richard Griesemer, who heads NCI's bioassay program, pointed out that the historical incidence of liver tumors in the male mouse is about 15%, which is above the incidence observed in the treated animals. Cipriano Cueto, NCI staff member, said that the study was considered to be inconclusive due to the poor animal survival which reduced the sensitivity of the study.

Wolfe's motion that the carcinogenicity of 1,1,1-trichloroethane cannot be determined because of the inadequacy of the study was approved unanimously.

**Proflavin.** The bioassay summary report states, "The unusually high incidence of hepatocellular carcinomas and hemangiosarcomas in control male mice and the unusually high incidence of malignant lymphomas in all groups of female mice in conjunction with the fact that a positive control carcinogen was tested in the same room with these animals raises a question of the validity of these bioassay results." NCI staff determined that the study was inconclusive; the subgroup agreed and recommended it be retested.

The two chemicals determined not to be carcinogenic:

**Phenformin.** The bioassay reported said that "tumors appearing in treated rats and mice were similar in type and number to those in controls, and

no pathologic or statistical evidence of induction of tumors in these species by phenformin was found. The motion by subgroup member Sheldon Samuels, AFL-CIO, that it was not carcinogenic under conditions of the test was accepted without objection.

**Dimethoate.** Brown commented that the study appeared to be straightforward and he agreed with the staff's conclusion that, under the conditions of the test, dimethoate did not demonstrate carcinogenicity. His motion to that effect was approved unanimously.

## SUSPECT CHEMICALS IN MANY PRODUCTS, INCLUDE CASTOR OIL, WITCHHAZEL

Thirty-eight chemicals, some recommended by the Clearinghouse and some by the Chemical Selection Working Group (NCI staff and representatives of other government agencies), have been approved by NCI's Chemical Approval Group for long term testing to determine if they are carcinogens. At about $250,000 each, cost of testing the 38 could reach $10 million.

The process of selecting chemicals for tests from the thousands that enter the environment each year is an involved one. NCI contracts with Stanford Research Institute to assist. Substances are nominated on the basis of chemical structure, similarity to known carcinogens, human exposure, foreign data, epidemiological clues, results of the short term in vitro (such as the Ames) tests.

The 38 newly selected chemicals include some used in pesticides, paints, solvents, drugs, flame retardants, herbicides, soaps and detergents, and rubber products, among others. Some are found extensively in water supplies and are prime suspects in the increased incidences of bladder cancer in those areas. The list includes the old home remedy, castor oil, which is used more extensively in paints, plastics and lubricants than as a pharmaceutical. And it includes witchhazel, used extensively in cosmetics, vitamins and hormones.

The chemicals and data on exposure and carcinogenic evidence:

**Bromoform (tribromomethane).** Use pattern: as chemical intermediate, for geological assaying, and as a solvent for waxes, greases, and oils. Formerly as a sedative and an antitussive. Bromoform has been identified by the EPA in water at 29 different geographical locations.

Carcinogenic evidence—Human data: When the molar concentrations in water of chlorodibromomethane, bromoform, and bromodichloromethane (as identified by the EPA) were added together and used as an exposure index in geographical correlation studies, they showed a stronger association than chloroform alone with certain cancer mortality rates, especially bladder cancer in males and females. The vapor has been reported to cause irritation of the respiratory tract, lacrimation, and liver damage. It is absorbed through the lungs, the gastrointestinal tract, and the skin. Short term tests: Although no mutagenicity tests or other short term tests were found in the published literature, bromoform has been observed to be active in the Ames' assay.

**1,2-Dichloropropane.** Used as an insecticide, generally in combination with other fumigant chemicals for treatment of stored grain. Controls various soil insects and peach tree borers. Recommended for use on apricots, nectarines, and peaches. When consumed as a part of a DD mixture, used as an insecticide on crops and for livestock. Reported by the EPA on its list of organic compounds identified in drinking water.

Carcinogenic evidence—Animal data: The tests reported were not of sufficient duration to reflect the carcinogenic potential. Both studies were by the inhalational route and no tumors were observed following a maximum observation time of one year. Short term tests: No mutagenicity tests were found. However, in one report, chromosome abnormalities (polyploidy, chromatid deletions, achromatic areas, and acentric fragments) were found in the bone marrow cells of rats given a single subcutaneous dose.

**Antimony oxide.** Used in flame retardant chloroparaffin-antimony oxide systems in which it acts as an afterglow inhibitor. Textile uses of these systems have been almost exclusively for outdoor canvas and cotton duck treatment for military products. Current growth is in the construction and automotive industries for flame retardant polymer products, especially electrical coatings. Recommended as a fire-retardant synergist in the presence of halogens for plastics, textiles, elastomers, and paints. Widely used as a paint pigment, in glass manufacture, and as a mordant.

Carcinogenic evidence—Human data: Inhalation can lead to irritation of the respiratory tract, eyes, nose, and throat; skin contact may result in dermatitis. Radiographic changes, without evidence of systemic toxicity, were found in the lungs of antimony-processing-plant workers. In another study, x-ray spectrophotometry detected up to 11 mg/cm$^2$ antimony oxide in the lungs of workers. Animal data: In a number of carcinogenicity experiments antimony oxide was given by various routes to various species. While no tumors were seen in any of these studies, they are judged inadequate because all animals were observed less than a year.

**Castor oil.** The 1971 U.S. consumption pattern for castor oil has been estimated as follows: for paint and varnish drying oils, 19%; for plastics and resins drying oils, 3%; for other drying oils, 13%; for manufacture of fatty acids, 8%; for lubricants and similar oils, 5%; and for other industrial uses, 52%. Miscellaneous applications include use for artificial leather, fatty alcohols, pharmaceuticals, and soaps and toilet preparations.

Carcinogenic evidence—Human data: Castor oil

has been reported to be a slight allergen following dermal application. Following ingestion, castor oil often causes griping, produces moderate irritation of the small intestine, pelvic congestion, and may also induce abortions. Animal data: The compound had been tested as a promoter in mice; the test was considered inadequate for evaluating tumor-promoting activity on the basis of the data reported.

**Diethanolamine (2,2-iminodiethanol).** A chemical intermediate in the synthesis of fatty alkanolamides, morpholine, and salts of fatty acids and alkyl sulfates used as emulsifiers. The 1973 U.S. consumption pattern for mono-, di-, and triethanolamines is estimated as follows: 37% for synthesis of soaps and detergents for textiles, toilet goods, metals, and other specialty surfactant uses; 22% for gas conditioning and petroleum uses; 20% exported; 5% for synthesis of morpholine; and 16% for miscellaneous applications including emulsion polishes and herbicides.

Carcinogenic evidence—Short term tests: No data on the mutagenicity of diethanolamine in mammalian or in the more commonly used microbial systems were found in the literature. However, in the bacteria xanthomonas phaseoli var. fuscans it was reported to be inactive in the induction of streptomycin resistance and phage resistance. These were qualitative tests, being spot tests carried out at a single dose.

**Gilsonite (uintaite).** Formerly used in the production of gasoline and related products, may find use in varnishes, paints, electrical insulators, molding compounds, paving materials, vulcanizing compounds, storage battery cases, brake linings, expanded rubber, automobile undercoatings, printing inks, paperboard additives, linoleum, floor tile, rust-preventive coatings, waterproof containers, expansion-joint sealers, oil-well drilling fluids, impregnant for exfoliated vermiculite, jet propellant, fire-retardant composition, insecticide composition, pipe insulation (thermal) and sealing compounds. The only commercially important deposits of gilsonite in the world are located in the Uintah Basin, in the northeast corner of Utah.

Carcinogenic evidence—Human data: Gilsonite has been reported to cause irritation by inhalation or dermal exposure and to cause photosensitization of the skin.

Gilsonite was selected for testing because of its large annual production, potential for human exposure, possibility of contamination by polynuclear aromatic hydrocarbons, and lack of carcinogenicity test data.

**Monuron (1,1-dimethyl-3-[p-chlorophenyl]-urea.** A broad-spectrum general herbicide used in the control of many annual and perennial grasses and herbaceous weeds on noncropland areas. Registered for nonselective weed control on noncropland areas (utility, highway, pipeline, railroad, and other right-of-way; petroleum tank farms, lymberyards, storage areas, industrial plant sites); and on irrigation and drainage ditchbanks. The 1975 estimated U.S. use pattern is as follows: agricultural uses, 16%; industrial and commercial, 68%; government agencies, 16%; and home and garden, 1%.

Environmental occurrence—Two studies on the persistence of monuron in the environment have been reported by EPA: In one study, persistence in soil and vegetation was estimated on the basis of residual phytotoxic activity. When applied at rates used to control crops or to eliminate vegetation on roadways, it remained for several seasons. Applied in higher concentrations (20-200 kg/hectare), it required up to three years to dissipate. In the second study on persistence in river water, monuron in acetone solution was found to dissipate by eight weeks.

**Nitrofurantoin (furadantin, furantoin).** Urinary tract antiseptic.

Carcinogenic evidence—Human data: One epidemiological report has observed an association (not necessarily a causation) between the consumption of the drug by pregnant women and adverse effects on fetal and neonatal functioning. A case report has noted that if flucose-6-phosphate dehydrogenase deficiency is present, nitrofurantoin administered during pregnancy may cause megaloblastic anemia in the fetus and newborn infant. Several adverse reactions have been noted in patients treated therapeutically with nitrofurantoin: Impaired pulmonary function, gastrointestinal distress, peripheral neuropathy, hemolytic anemia, anaphylaxis, acute polyneuritis, jaundice, and maculopapular erythematous eruption. Animal data: Reported inactive as a carcinogen in female rats fed 0.3% of diet for 36 or 44.5 weeks and observed an additional 17-20 weeks. In a 75-week feeding study (total dose 9.25g) with an additional five weeks of observation, breast tumors occurred in 19 of the 36 tested rats and in 12 of the 30 control rats. These tests are judged inadequate to ascertain the carcinogenicity of this compound.

**Phenylbutazone.** Used in medicine as anti-inflammatory agent possessing analgesic, antipyretic, sodium retention and mild uricosuric properties. Also used for treatment of gout, several forms of arthritis, thrombophlebitis, and local inflammatory conditions. Dosage ranges from 100 to 600 mg daily, usually for a week to 10 days; there could also be chronic dosing.

Carcinogenic evidence—Human data: Various forms of leukemia were reported in patients who had received phenylbutazone. The evidence is, however, insufficient to relate the use of this drug and subsequent development of leukemia.

**Tert-butyl alcohol (2-methyl-2-propanol, t-butanol).** A chemical intermediate in the manufacture of rubber products, oil-soluble polyester resins, and perfumes, octane improver in gasoline and a component in industrial cleaning compounds. Environmental occurrence: Has been reported by EPA to occur in drinking water.

Carcinogenic evidence—Animal data: In one study the incidence of skin tumors was not significant in mice given repeated topical treatments with tert-butyl alcohol following topical application with 4-nitroquinoline-1-oxide. These negative results were not considered conclusive since positive controls were not included in the experiment.

**Witchhazel (hamamelis extract, spotted alder).** Distilled (aqueous) extract of witchhazel is used as a mild astringent in cosmetic preparations (skin tonics, eye lotions, aftershave lotions) and in some drug products (vitamin and hormone preparations for external use). The more astringent alcoholic extract is used in drug products (e.g., ointments for hemorrhoids).

**Agaritine.** An ingredient of the mushroom which is a regular food supply eaten by large segments of the population either cooked or semicooked.

Carcinogenic evidence—37 hydrazine derivatives are known to induce tumors in laboratory animals.

**2,4-dichlorophenol (2,4-dichloro-hydroxybenzene).** A chemical intermediate in the manufacture of herbicides, bacteriostats, fungistats, germicides, and dyestuffs. Environmental occurrence: Has been detected in water supplies by EPA in four different geographical locations.

Carcinogenic evidence—Animal data: Has been shown to have promoting activity on mouse skin initiated with DMBA in benzene.

**N-phenyl-β-naphthylamine (PBNA, phenyl-2-naphthylamine).** Mostly used as an antioxidant in rubber where it can comprise as much as 1% of the finished product. Also used as an antioxidant for greases and oils, as a stabilizer during manufacture of synthetic rubber, and as an intermediate in the synthesis of dyes as well as other antioxidants.

Carcinogenic evidence—Human data: An epidemiologic study, involving deaths among workers who entered the rubber industry after 1949 (when BNA was replaced by PBNA), shows no significant excess risk of bladder tumors in the industry when compared to the general population. The authors point out, however, that their data is not conclusive. Animal data: Several studies were reported. Mice given repeated subcutaneous injections of the compound showed no tumors after 22 months, and three dogs fed N-phenyl-β-naphthylamine daily had no tumors after 4.5 years. In another study, the lymph, lung, and liver tumor incidence in mice given the chemical orally was slightly elevated over controls, but the authors stated that further testing is required to clarify the results.

**N-butyl-chloride.** Used as a chemical intermediate, a solvent, and a veterinary anthelmintic.

Carcinogenic evidence—Animal data: In one recent study, no significant increase in lung tumor incidence was observed in strain A mice 24 weeks following intraperitoneal administration. A slight but significant increase was noted for sec- and tert-butyl chloride in the same experiment. Other biological properties: Animal experiments suggest a low toxicity. Oral LD50:2670 mg/kg in the rat. Dogs tolerated an oral dose of 11 ml/kg without toxic effects. The lowest inhalation concentration of n-butyl chloride reported to produce toxic effects in rats was 8000 ppm (4 hour exposure). Central nervous system depression was noted during intoxication. Structure/activity relationships: As a linear, four carbon alkyl chloride, n-butyl chloride is a potential alkylating agent but is not expected to be as active as the shorter chain or branched alkyl chlorides.

Selected for test because it is a model alkyl chloride of particular structural interest and because of its potential for human exposure.

**Oleic acid-diethanolamine condensate (amine/acid ratio=1/1) (oleic acid diethanolamide).** Used primarily in the cosmetics industry as a foam stabilizer, thickener, and superfatting agent in shampoos and bubble bath.

Carcinogenic evidence—Structure/activity relationships: Oleic acid and methyl oleate have been reported to be weakly active as tumor promoters in mouse skin.

Selected for testing because of its high annual production, potential for human exposure, and lack of adequate carcinogenicity tests. A recommendation was made for a skin-painting test.

**Lauric acid-diethanolamine condensate (amine/-acid ratio=1/1) (lauric acid diethanolamide).** Used primarily as a foam stabilizer in liquid household detergents and as a shampoo thickener. It is also used as a dispersing agent for both agricultural sprays and pigments.

Carcinogenic evidence—Structure/activity relationships: Lauric acid has been reported to be weakly active as a tumor promoter in mouse skin.

Selected for testing because of its high annual production, potential for human exposure, and lack of adequate carcinogenicity tests. A recommendation was made for a skin-painting test.

**Coconut oil acid-diethanolamine condensate (amine/acid ratio=2/1) (coconut oil acid-diethanolamide).** Coconut oil-diethanolamine condensate is used primarily as a foan stabilizer in liquid detergents, though it also acts as a soil suspender, dispersant, wetting and scouring agent, and as a booster in other household detergents and industrial cleaners. It is used in the cosmetics industry as a thickener and softener in bubble bath, soaps, and shampoos.

**Pyridine (azabenzene, azine).** Estimated 1975 U.S. consumption pattern is as follows: exports (primarily to the United Kingdom for the production of the herbicides diquat and paraquat), 50%; solvent and reagent uses, 16%; manufacture of antihistamines and anti-infectives, 13%; manufacture of piperidine, 7%; manufacture of textile waterproofing agents, 7%; and miscellaneous uses (e.g., flavoring agent) 7%. Environmental occurrence: In Russian studies, pyridine was

detected in the working area around coke furnaces, and in agricultural crops and fish. Pyridine has been detected in four different water supplies by EPA.

Carcinogenic evidence—Animal data: In one study, rats received subcutaneous injections of from 3-100 mg/kg pyridine twice weekly for one year. The animals were autopsied at either 12 or 18 months and no statistically significant carcinogenic effect was observed compared to control groups of both saline injected and untreated rats. The significance of these results is questionable due to the high incidence (95-100%) of testicular tumors observed in both treated males and controls, although the authors reported this was not uncommon for the strain of rats tested.

**8-hydroxyquinoline (8-quinolinol, phenopyridine).** Used as an antimicrobial drug in human medicine for treatment of minor burns and hemorrhoids, and is reportedly used as a bacteriostatic additive in hairdressing preparations to control dandruff. Because of its chelating ability it finds use as an analytical colorimetric reagent and for the precipitation and separation of metals. It can also be used for the synthesis of a number of dyes.

**Decabromodiphenyl oxide (decabromobiphenyl ether, DBDPO).** Has had minimal use as a flame retardant additive in thermoplastic resins. Presently being considered as a fire retardant additive in synthetic fibers.

Carcinogenic evidence—Human data: No epidemiological studies or case reports associating decabromodiphenyl oxide exposure with an increased risk of cancer in humans were found in the literature. Application of a 5% suspension in petrolatum, three times per week for three weeks, did not result in skin sensitization.

**Benzene (benzine, benzol).** Estimated 1974 U.S. consumption pattern is as follows: 46% for ethylbenzene, 23% for phenol, 16% for cyclohexane, 5% for aniline, 4% for maleic anhydride, 2% for detergent alkylate, and 4% for other uses. Environmental occurrence: Benzene has been measured in water supplies by EPA 47 different times. The highest concentration of benzene reported was 10$\mu$g/l. Benzene has also been detected in air, with the most important sources of emissions from gasoline evaporation at the fuel pump and from coke ovens. Total emissions of benzene are estimated to be 1.149 millions pounds per year.

Carcinogenic evidence—Human data: The association between long-term benzene exposure and the occurrence of leukemia has been suggested by numerous studies dating back to 1928. However, most studies do not contain adequate information on degree of exposure or size of population at risk. In addition, workers in benzene-related occupations were probably exposed to other chemicals.

**Chlorpheniramine maleate (chlorpheniramine, Chlor-Trimeton).** As an antihistamine in human and veterinary medicine and in proprietary antitussive formulations. A dose level of 2 mg. for human use in over-the-counter drug preparations is currently allowed.

Carcinogenic evidence—Human data: It can be extremely toxic in humans; therapeutic doses have produced sedation, dizziness, anorexia, nausea, headache, polyuria, diplopia, dysuria, and rarely, dermititis. Aplastic anemia and thrombocytopenic purpura have also been attributed to chlorpheniramine maleate therapy.

**O-phenylphenol (biphenylol, dowicide 1).** Used as a citrus fungicide and a germicide. In the past it has been used on vegetables. Other uses include as an intermediate in wear-resistant surface coatings and as a dip for crates, hampers, and impregnation of fruit wraps.

Carcinogenic evidence—Human data: O-phenylphenol is moderately toxic when ingested or inhaled; however, it is not absorbed through the skin in acutely toxic amounts. It is an irritant when inhaled as a dust or applied to the skin in aqueous solutions above 0.5%. Corneal necrosis may result from contact with liquid or dust forms. A fatal oral dose of 10 mg has been reported, and two cases have described toxic effects on the urothelium of the bladder in humans. Animal data: Several carcinogenicity tests have been reported. In one limited study, rats received the compound at a level of 0.02 to 2% of the diet and occasional tumors not thought to be associated with treatment were seen; the survival rate for the animals in this experiment was unsatisfactory (less than 50% at one year).

**Chlorodibromomethane (dibromochloromethane).** No evidence was found that it is used as other than a laboratory chemical. Environmental occurrence: Chlorodibromomethane is a commonly observed contaminant found in water supplies. Its concentration has been reported by EPA to be as high as 100.0$\mu$g/l in some areas and it has been found in the water at 61 different geographical locations.

Carcinogenic evidence—Human data: When the molar concentrations in water of chlorodibromomethane, bromoform, and bromodichloromethane (as identified by the EPA) were added together and used as an exposure index in geographical correlation studies, they showed a stronger association than chloroform alone with certain cancer mortality rates, especially bladder cancer in males and females.

**Bromodichloromethane.** Used as a chemical intermediate, solvent, and flame retardant. Environmental occurrence: Measured in U.S. drinking water in concentrations of at least 116.0 mg/l; has been identified in water samples 66 times.

Carcinogenic evidence—Human data: When the molar concentrations in water of chlorodibromomethane, bromoform, and bromodichloromethane were added together and used as an exposure index in geographical correlation studies, they showed a stronger association than chloroform alone with

certain cancer mortality rates, especially bladder cancer in males and females. Short term tests: No mutagenicity or other short term tests were found. However, it has been reported to be mutagenic in the Ames tester strains.

Selected for testing because of its structure, lack of carcinogenicity data on brominated methanes and potential for human exposure in drinking water.

**Xylenes, mixed (dimethylbenzenes, xylol).** The 1974 U.S. consumption pattern for mixed xylenes has been estimated as follows: for production of isomers, 66%; ethylbenzene, 6%; as a solvent in the paint industry, 9%; other solvent uses, 9%; and blended in gasoline and for production of miscellaneous derivatives, 10%. Environmental occurrence: Reported by EPA on its list of organic compounds identified in water.

Carcinogenic evidence—Human data: One epidemiologic study has associated death from lymphatic leukemia in rubber workers with exposure to solvents (including xylene, toluene, trichloroethylene, and various aliphatic hydrocarbons). Toxic effects in humans following acute and/or chronic exposures include: narcosis, liver, kidney, and heart damage, and aplastic anemia. The mean lethal dose of xylene is not known, and no fatal cases have been recorded. Eye irritation has been reported for exposure to xylene vapor.

**Sodium fluoride (fluorol, pergantere).** Used primarily for water fluoridation, but is being replaced by cheaper silicofluorides in this application. Additional applications include use as a dental caries prophylactic, in insecticides, in fungicides, and in fluxing agents. Environmental occurrence: A level of 1 ppm fluoride is normally used to fluoridate drinking water. Normal ground water levels are generally less than 1 ppm. Fluorides have also been detected in air samples in urban areas.

Carcinogenic evidence—Human data: An examination by NCI scientists of trends in cancer death rates in the U.S. (1950-69) has failed to produce evidence linking fluoridation of public water supplies to cancer. High oral doses of sodium fluoride are acutely toxic; doses of 25 to 50 mg can cause severe gastrointestinal distress. From numerous case studies, a lethal dose of 75-150 mg/kg has been estimated. Chronic exposures, due to high concentrations of natural fluoride ion in water, produce mottling of the teeth, osteosclerotic changes in the skeleton, kidney damage, and sometimes nervous system damage.

**Rotenone (derrin, noxfish, nicouline).** Insecticide for home and garden use and fish toxicant.

Carcinogenic evidence—Human data: Derris root and other rotenone preparations have caused dermatitis in humans, and an estimated fatal oral dose is 140 to 1,480 mg. Animal data: Rotenone induces slow growing, non-metastatic, mammary fribroadenomas in albino rats. 1.7 mg/kg for 40 days gave 100% incidence of such tumors in an unspecified strain of rat, while the same dose in Wistar rats gave 50% incidence.

**Oxalic acid.** The 1972 U.S. consumption pattern for oxalic acid has been estimated as follows: for textile finishing, stripping, and cleaning, 27%; for metal and equipment cleaning, 27%; as a chemical intermediate, 25%; for leather tanning, 2%; and for miscellaneous applications, 19%. Miscellaneous applications include its use as an additive for breaking water-in-oil emulsions, as a purifier for crude natural gums, and as an additive in soil treatments. Environmental occurrence: Oxalic acid is reported to be found in the water in at least one geographical location in the U.S. according to an EPA study. This compound is found in a number of plants, such as spinach, rhubarb, beet leaves, black tea, and cocoa. Low levels are also found in common fruits and vegetables.

Carcinogenic evidence—Human data: As a severe irritant, oxalic acid is highly toxic and corrosive by oral, dermal or inhalational administration. The lowest reported oral lethal dose in humans is 100 mg/kg, and with higher concentrations death may occur within minutes.

**Tetrakis(hydroxymethyl)phosphonium chloride (THPC) and sulfate (THPS).** These chemicals were selected for test after a review of the flame retardant class. This chemical is used to treat cotton and other natural fibers. The annual production is around 2 million pounds and is a widely used flame retardant. EPA expressed concern because of reports from the USSR where this flame retardant is banned. The CSWG voted unanimously to recommend these chemicals for test because of widespread use as a flame retardant, potential for human exposure, suspect structure, lack of previous chronic testing and concern of EPA.

**Chlorendic acid.** This chemical was also selected after the flame retardant class review. Approximately 10 million pounds of this acid are produced annually and EPA is concerned about the weathering properties of this compound and the possibility of the free acid being released into the environment. The CSWG unanimously voted to recommend this chemical for test because of its suspect structure, lack of previous testing, large annual production, potential for human exposure and indication from EPA that they would like to see this chemical tested for carcinogenicity.

**Chlorowax 40 and chlorowax 500C.** These chemicals were selected for test after review of the flame retardant class. They had been nominated earlier by FDA because these two compounds are representative examples of chlorinated paraffins which are significant industrial chemicals with increasing use as flame retardants, in plastics and as cutting oil additives. The CSWG unanimously voted to select these two chemicals for test because of their significance as industrial chemicals, widespread use as flame retardants, large annual production (around 61 million lbs.)

lack of previous testing for carcinogenicity and the possibility for bioaccumulation in fatty tissue.

**N,N-dimethyldodecylamine oxide.** This chemical was selected for test by the CSWG after an extensive review of the amine oxide subclass of the larger soaps and detergents class.

**Chloroacetophenone and chlorobenzalmalononitrile.** These chemicals were nominated by the Dept. of Defense because of their widespread use in training the armed forces and as riot control agents. The CSWG also discussed the recent widespread interest in these chemicals in relation to their potential hazard to policemen. The CSWG unanimously voted to select these chemicals for test because of their widespread use as riot control agents by the federal government and other law enforcement agencies, suspect structure, lack of adequate testing for carcinogenicity, and DOD's and NIEHS's concern about the safety of these compounds.

## UPTON, JOB FINALLY CONFIRMED, SAYS HE WASN'T HIRED TO PUSH PREVENTION

The White House personnel office, after saying early last week that it would need two more weeks to process Arthur Upton's appointment as NCI director, suddenly found it didn't need that much time and made the appointment official Friday. Several exasperated phone calls, one of which was said to have been placed by NIH Director Donald Fredrickson, may have prompted the action, delayed unnecessarily since April.

Upton's first move was to call a press conference, which brought about one of the rare appearances of the lay press at NCI. Predictably, those newspersons honed in on the currently popular issues of laetrile, saccharin and prevention.

Upton said in response to their questions that:

- Ethical issues involved in administering an agent with no demonstrable efficacy to patients would have to be resolved before he would approve clinical tests.
- He could forsee "some benefit" from delaying FDA's ban on saccharin for 18 months, as proposed by legislation Congress is considering. "Human epidemiological data has shown a small risk. That data has been challenged. Perhaps in 18 months it could be nailed down." Also, Sen. Edward Kennedy has suggested that saccharin manufacturers, who claim the benefits of the sweetener outweigh the risks, should provide evidence supporting that claim, and that possibly could be done in 18 months, Upton noted.
- Prevention does deserve more emphasis. But "my appointment does not signify a desire to push the institute in a particular direction, or at least I was not made aware of that by anyone in the Administration."

"That is one of the most important questions we face, and one I'm not prepared to deal with today," Upton said when asked what he would cut back to allow for expansion of environmental carcinogenesis or other studies. "Clearly, if the public is determined that we cannot or will not spend more for cancer, rearrangement or redeployment will be required to fund any new emphasis. But it must be done with great care. We must make certain that the best science, the most promising research, is employed in all areas. High quality research should not be sacrificed anywhere."

Upton said he did not think NCI has been spending money wastefully. "To the contrary, there are initiatives for which we could use additional money."

Asked if NCI has spent too much money on virus research, Upton said it is "too early to decide" if viral vaccines will be developed to help control cancer. "I have no reason to predict it won't happen. On the contrary, in some human cancers, I feel viruses are implicated."

## CONTRACT AWARDS

**Title:** Radiologic Physics Center, renewal
**Contractor:** Allegheny General Hospital, Pittsburgh, $380,123.

**Title:** Human melanoma: Evaluation of BCG immunotherapy of patients without detectable disease after removal of tumor containing lymph nodes
**Contractor:** UCLA, $55,454.

**Title:** Computer support for cancer information dissemination
**Contractor:** IIT Research Institute, $1,320,427.

**Title:** Clinical evaluation of the use of computerized transaxial tomography in the diagnosis of brain tumors, continuation
**Contractor:** George Washington Univ., $77,801.

**Title:** EPA/NCI special skin cancer epidemiology study
**Contractors:** Univ. of Utah, $34,060; and Geomet Inc., $132,870.

## SOLE SOURCE NEGOTIATIONS

*Proposals are listed here for information purposes only. RFPs are not available.*

**Title:** Operation of the Louisiana Tumor Registry
**Contractor:** Charity Hospital of Louisiana at New Orleans.

—*Editor* JERRY D. BOYD

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