interactions with sulfated glycoconjugates on host cells.

The role of the Division of Cancer Biology, Diagnosis and Centers (DCBDC) of the National Cancer Institute (NCI) under the CRADA will include the following:

1. The government will continue preclinical development of the peptides and mimetics as inhibitors of tumor growth and metastasis *in vitro* and *in vivo*. Data from these studies will be provided to the pharmaceutical company and evaluated jointly.

2. The government will provide available data and expertise in structure-function relationships and conformational analysis of the active peptides and peptidomimetics. These data will be evaluated jointly in order to assess an efficient research path.

3. As appropriate, the government will initiate collaborative clinical trials under its extramural clinical trials network, thus ensuring the clinical evaluation of the compounds.

4. Relevant Patent rights are available for licensing through the Office of Technology Transfer, NIH. For further information contact: Ms. Carol Lavrich, Technology Licensing Specialist., Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Rockville, Maryland 20852–3804. (301) 496–7735 (ext. 287), Fax (301) 402–0220. There is no deadline by which license applications must be received. *See* 35 U.S.C. 207 and 37 C.F.R. Part 404.

The role of the successful pharmaceutical company under the CRADA will include the following:

1. Prepare and characterize GMP quality nonmetabolizable, analogs (as determined by both parties) of the active peptides and provide these to the DCBDC, NCI for characterization as angiogenesis and metastasis inhibitors.

2. Provide funds for preclinical development of the peptides *in vitro* and for screening activities in appropriate animal models.

3. Collaborate in the planning and support for clinical development leading to FDA approval and marketing.

Criteria for choosing the pharmaceutical company include the following:

1. Experience in preclinical and clinical drug development.

2. Experience and ability to produce, package, market, and distribute pharmaceutical products in the United States.

3. A willingness to cooperate with the Public Health Service in the collection, evaluation, publication, and maintenance of data from clinical trials of investigational agents.

4. A willingness to cost share in the development of heparin binding peptides as outlined above. This includes acquisition of material and synthesis of heparin binding peptides and/or peptidomimetics in adequate amounts as needed for future clinical trials and marketing.

5. An agreement to be bound by the DHHS rules involving human and animal subjects.

6. The aggressiveness of the development plan, including the appropriateness of milestones and deadlines for preclinical and clinical development.

7. Provisions for equitable distribution of patent rights to any inventions arising under the CRADA. Generally the rights of ownership are retained by the organization which is the employer of the inventor, with (1) an irrevocable, non-exclusive, royalty-free license to the Government (when a company employee is the sole inventor) or (2) an option to negotiate an exclusive or non-exclusive license to the company on terms that are appropriate (when a Government employee is the sole inventor).

Dated: December 22, 1994.

Karen Maurey,

Acting Director, Office of Technology Development, National Cancer Institute, National Institutes of Health.

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BILLING CODE 4140–01–P

Public Health Service

National Toxicology Program; Announcement of Intent To Conduct Toxicological Studies of 16 Chemicals

Request for Comments: As part of an effort to inform the public, the National Toxicology Program (NTP) routinely announces in the **Federal Register** the lists of chemicals for which plans to develop protocols for Toxicological studies are underway. This announcement will allow interested parties to comment and provide information on chemicals under consideration. Chemicals and types of studies under consideration are listed below.

Chemical 1. 2-Cyclohexene-1-one (CAS No. 930–68–7) 14-day, 13-week and 2-year toxicology and carcinogenesis inhalation studies.

2-Cyclohexene-1-one (2–CHX–1) belongs to a class of chemicals termed alpha, beta-unsaturated ketones. This class of chemicals was nominated by National Cancer Institute for carcinogenicity and mechanistic toxicity studies with high priority due to demonstrated human industrial and consumer exposure and inadequate health effects testing. 2–CHX–1 is being studied as an example of a cyclic member of the class of aliphatic alpha, beta-unsaturated ketones. It is used as an industrial chemical intermediate in the chemical, pharmaceutical, and agricultural chemical industries. It is used in the synthesis of resorcinol, phenol, 11-deoxy-prostaglandins, immunostimulants, anti-inflammatory agents, fungicides and herbicides. Consumer exposure includes the use of 2–CHX–1 in low-odor permanent wave hair preparations, antifungal agents and mold inhibitors for bread storage containers, smoke flavor preparations, and detergents. 2–CHX–1 is present in tobacco smoke and is present in side-stream smoke from tobacco combustion. Natural occurrence of 2–CHX–1 includes wild rice fermentation products, a component of beech wood and roasted coffee. 2–CHX–1 may also be present in foods and consumer products as an impurity in the flavor enhancer tetrahydronaphthalenone. The major effect reported on the toxic effects of 2–CHX–1 in animals is the depletion of glutathione in various tissues of rodents. 2–CHX–1 is a weak, direct acting mutagen in the Salmonella assay and in a rat hepatocyte/DNA repair test. 2–CHX–1 was able to react covalently with deoxyguanosine.

Chemical 2. Methyl Vinyl Ketone (CAS No. 78–74–4) 14-day, 13-week and 2-year toxicology and carcinogenesis inhalation studies.

Methy Vinyl Ketone (MVK), a member of the class of chemicals termed alpha, beta-unsaturated ketones, was nominated by the National Cancer Institute for carcinogenicity and mechanistic toxicity studies with high priority due to demonstrated human industrial and consumer exposure and inadequate health effects testing. MVK was selected as the prototype non cyclic member of the major class of straight-chain aliphatic alpha, beta-unsaturated ketones. MVK is used commercially in the production of pesticides, perfumes, plastics and resins. It is a pharmaceutical intermediate in the synthesis of steroids, vitamin A, and anticoagulants. Consumer exposure to MVK is widespread due to its presence in cigarette smoke, its production by gamma-irradiation from sugars in tropical fruit, and as a ubiquitous air pollutant due to its presence in vehicular exhaust. MVK is an alkylating agent and may interact with DNA to form covalent adducts. MVK was reported by the NTP to be mutagenic in the Salmonella assay.

Chemical 3. Ethyl vinyl ketone (CAS No. 1629–58–9) 14 and 90-day inhalation toxicity studies in F344 rats and B6C3F1 mice.

Ethyl vinyl ketone (EVK) is a secondary conjugated carbonyl compound from the subclass of aliphatic alpha, beta-unsaturated ketones, and has a wide distribution in the environment, particularly in foods. EVK is a component of the semi-volatile fraction of cigarette/tobacco smoke and is a volatile organic compound linked to odor and taste problems associated with water purification and fish breeding. Consumption in foods and beverages also represents a broad but very low level route of human exposure. The principal use of EVK is as a natural and synthetic flavoring agent in orange aqueous essence and oils for flavor and aroma enhancement, especially of frozen orange juice concentrates. The limited available test data on this compound include demonstrations of positive mutagenicity and the formation of DNA-damaging adducts. These data support the possibility that EVK may pose a mutagenic and carcinogenic risk to humans.

Chemicals 4 & 5. Trimethoprim/Sulfamethoxazole (CAS No. 8064–90–2) 13-week and 2-year dosed-feed studies in F344 rats and B6C3F1 mice.

Trimethoprim/Sulfamethoxazole (TMP/SMZ) (Bactrim®) is a chemical combination used to treat urinary tract infections and pneumonia. TMP/SMZ was nominated by the National Cancer Institute for carcinogenicity and neurotoxicity testing based on significant human exposure and the potential for increased use in the treatment of pneumonia in AIDS patients. In addition, because TMP/SMZ appears to exhibit antifolate activity, the role of folate deficiency in possibly enhancing the known carcinogenicity of Sulfamethoxazole may need to be investigated. A study to screen for TMP/SMZ reproductive/developmental toxicity effects was done as a part of the NIEHS AIDS Program.

Chemical 6. Dicyclopentadiene (CAS No. 77–73–6) 13–week and 2-year studies in F344 rats and B6C3F1 mice.

DCPD was nominated by the National Cancer Institute for evaluation of carcinogenicity and reproductive toxicity. DCPD is a high production chemical, with over 130 million pounds produced annually and over 43 million pounds imported in 1988. The nomination was based on the high and increasing production volume, the presence of DCPD in ground and surface water near sites where it is used, limited data on the hazards associated with subchronic exposure, and the absence of data on the hazards associated with long term exposure. DCPD is currently being evaluated in the NTP Continuous Breeding Protocol and Teratology protocols (gavage studies).

Chemical 7. Ethyl cyanoacrylate (CAS No. 7085–85–0) short-term inhalation studies.

Ethyl cyanoacrylate (ECA) was nominated by the Consumer Products Safety Commission. ECA is the major component of instant setting adhesives widely available in retail stores and there is widespread potential consumer exposure. There is potential occupational exposure to ECA vapors that exists wherever ECA glues are used for assembly, in packaging, or other adhesive applications. Irritant dermatitis and eye irritation in workers has been reported. There is one report of women occupationally exposed to ECA vapors giving premature birth to babies with malformations. There is very little toxicological data and no carcinogenicity data available for this chemical. A related chemical, isobutyl cyanoacrylate, is now used for medical applications because it does not produce formaldehyde during degradation as does the ECA. Evaluation of developmental and reproductive toxicity, neurotoxicity, and evaluation of carcinogenicity, using the inhalation route, have been recommended.

Chemical 8. Methylene Blue (CAS No. 7220–79–3) two-year toxicity/carcinogenesis and toxicokinetic gavage studies in F344 rats and B6C3F1 mice.

Methylene Blue (MB) was nominated for carcinogenicity testing by the National Cancer Institute (NCI) based on the widespread use of this compound and the potential for high exposure in animals and humans. Methylene blue is used therapeutically in the treatment of methemoglobinemia and cyanide poisoning. Other reported medicinal uses of MB have included the management of chronic urolithiasis and treatment of cutaneous viral infections as well as the treatment of manic-depressive psychosis. As a dye/stain, MB is used in surgical and medical marking, as an indicator dye, a bacteriologic stain, a food colorant and a dye for cotton and wool. Data from the National Occupational Exposure Survey (NOES) indicate that 69,563 workers, including 42,026 female employees, were potentially exposed to methylene blue between 1981 and 1983. In four-week and 13-week gavage toxicity studies conducted by NTP, the hematopoietic system was the major target of MB toxicity. Dose-related hemolytic anemia was seen in all of the groups treated with MB. Increased methemoglobin formation, decreased hematocrit, increased in reticulocyte production, splenomegaly, and increased Heinz body formation were seen in rats and mice of both sexes exposed to MB. Histologically, there was hyperplasia of the bone marrow in response to the anemia.

Chemical 9. Butanal Oxime (CAS No. 110–69–0) 14-day and 90-day prechronic dosed water toxicity studies in F344 rats and B6C3F1 mice.

Butanal oxime was nominated for toxicity and carcinogenicity evaluation by the National Cancer Institute. Along with methyl ethyl ketoxime and cyclohexanone oxime, butanal oxime is part of an oximes class study. Cyclohexanone oxime and methylethyl ketoxime have been studied in NTP 90–day drinking water toxicity studies in rats and mice, and industry sponsored inhalation carcinogenicity studies of methyl ethyl ketoxime have been completed. Unlike the other oximes, butanal oxime metabolism results in the release of cyanide, and is therefore expected to have a different toxicological profile. There is limited toxicology information available on butanal oxime.

Chemical 10. Cyclohexene Oxide (CAS No. 286–20–4) 28-day, 13-week, and 2-year topical and/or gavage toxicity/carcinogenesis studies in F344 rats and B6C3F1 mice.

Cyclohexene Oxide (CHO) was nominated by the National Cancer Institute for carcinogenicity, toxicity, and mechanistic studies as a representative cycloalkene monoepoxide which is produced in substantial annual volumes with potential human exposures. CHO is found widely in natural products, pharmaceuticals, and agricultural chemicals and, it has a wide range of uses, including the production of other chemicals and as a laboratory reagent. It is primarily used as an industrial raw material in organic synthesis of various chemical intermediates for a wide range of industrial products and there is the potential for worker exposure. In addition, a survey identified CHO in the drinking water of two of 17 municipalities suggesting the potential for more widespread exposure to the general population. CHO has a low acute toxicity in rats and rabbits, is a severe eye irritant, and is a moderate skin irritant. It is also a weak to moderate mutagen. There is minimal chronic toxicity information available.

Chemical 11. p-tert-Butylcatechol (CAS No. 98–29–3) 14-Day and 13-week dosed-feed studies.

p-tert-Butylcatechol (TBC) was nominated for carcinogenicity studies by the National Cancer Institute based

on high and increasing level of production and usage, potential for human exposure, suspicion of carcinogenicity, and interest in evaluating the toxicity of the dihydroxybenzenes chemical class of antioxidants. In 1989, U.S. production of TBC was reported to be 1.5 million lbs. TBC is used primarily as an antioxidant and stabilizer and there is potential for worker exposure. Consumer exposure occurs through TBC contamination of, and subsequent leaching from PVC products and other plastics and rubber products and from contact with Thermofax® duplicating papers. In addition, TBC is also being considered as a replacement for BHT and BHA, two chemicals used as food additives because of their antioxidant properties, but which have been found to be carcinogenic in rodents at high levels. TBC as well as BHA and BHT are non-mutagenic.

Chemical 12. Diisopropylcarbodiimide (CAS No. 693–13–0) 2-year carcinogenesis studies in F344 rats and B6C3F1 mice.

Diisopropylcarbodiimide together with Dicyclohexylcarbodiimide were nominated as representatives of the carbodiimide chemical class by the National Cancer Institute because of widespread potential exposure to personnel in biomedical laboratories and pharmaceutical and chemical industries, the lack of adequate toxicity data, and the suspicion of carcinogenicity because it is an alkylating agent. Both chemicals are potent sensitizers and have produced severe contact dermatitis, severe eye irritation, and delayed-onset temporary blindness. Fourteen-day topical studies have been completed and 90-day topical exposure studies are underway in F344 rats and B6C3F1 mice.

Chemical 13. Dicyclohexylcarbodiimide (CAS No. 538–75–0) 2-year carcinogenesis studies in F344 rats and C6C3F1 mice.

Dicyclohexylcarbodiimide together with Diisopropylcarbodiimide were nominated as representatives of the carbodiimide chemical class by the National Cancer Institute because of widespread potential exposure to personnel in biomedical laboratories and pharmaceutical and chemical industries, the lack of adequate toxicity data, and the suspicion of carcinogenicity because it is an alkylating agent. Both chemicals are potent sensitizers and have produced severe contact dermatitis, severe eye irritation, and delayed-onset temporary blindness. Fourteen-day topical studies have been completed and 90-day topical exposure studies are underway in F344 and B6C3F1 mice.

Chemical 14. Dimethyl adipate (CAS No. 627–93–0) 13-week and 2-year toxicity/carcinogenesis studies in F344 rats and B6C3F1 mice.

Dimethyl adipate (DMA) was nominated to the NTP for study by the Consumer Products Safety Commission (CPSC) because of widespread consumer exposure. Its primary consumer use is as a replacement for methylene chloride in paint strippers, along with other dibasic esters such as dimethyl glutarate and dimethyl succinate. This use is expected to increase because the standards for methylene chloride exposure are under review by regulatory agencies and new more stringent ones may be established. There is the potential for workers to be occupationally exposed to DMA and systemic exposure is primarily by inhalation of an aerosol or through percutaneous absorption. There is limited toxicity information available on DMA. NTP is coordinating its plans to conduct studies for this chemical with the Environmental Protection Agency and the Interagency Testing Committee.

Chemical 15. 2,3-Butanedione (CAS No. 431–03–8) 13-week and 2-year toxicity/carcinogenesis studies in F344 rats and B6C3F1 mice.

2,3,-Butanedione was nominated by the National Cancer Institute based on widespread human exposure and suggestive evidence of carcinogenicity from preliminary animal studies and genetic toxicity studies. The chemical is the parent compound of the a-diketones chemical class. The annual production of 2, 3-butanedione is less than 1 million pounds, and it is used in manufacturing processes and as a food (flavoring) additive. It was estimated in 1983 that 3,437 workers were potentially exposed to 2,3-butanedione in the workplace. Its widest exposure is through its natural occurrences in a wide variety of foods, including dairy products (5.9 ppm), meats, baked goods (44 ppm), produce, candy (21 ppm), and beverages (in coffee at levels up to 10 ppm), and is used as a flavor additive in foods. It is also a constituent of tobacco smoke. 2,3-Butanedione is also a bacterial mutagen. There was no information on the effects of chronic exposure to 2,3-Butanedione in the open literature.

Chemical 16. Methyl styryl ketone (CAS No. 122–57–6) 13-week and 2-year toxicity/carcinogenesis studies in F344 rats and B6C3F1 mice.

Methyl styryl ketone (MSK) was nominated by the National Cancer Institute based on its potential for human exposure. MSK is an apha, beta-saturated ketone that was produced at <1,000,000 lbs in 1989 (>55,000 lbs were imported in 1993) and is also present as a natural product. It is used as an intermediate in organic syntheses and in other industrial applications, and is a flavoring and fragrance additive in many products, including cosmetic products (soaps (50–100 ppm), creams and lotions (50–100 ppm), and perfumes (50–500 ppm); food products (baked goods (5.2 ppm) and candy (4.4 ppm)). It was recently identified as a flavoring additive to cigarettes, but its level of use was not reported. It occurs naturally in essential oils of flowers, as a pyrolysis product in waste gases resulting from the removal of coating materials in recycling processes, and as an ozonization product of the humic substance, p-hydroxybenzaldehyde. It has been estimated that 5,483 workers were potentially exposed to MSK in the workplace in 1983. MSK has been identified in wastewaters, and has been shown to bioaccumulate in blue crabs in the southern Chesapeake Bay. MSK is a bacterial mutagen. There was no information on the effects of chronic exposure to MSK in the open literature.

Anyone having relevant information (including ongoing toxicological studies, current or future trends in production and import, use pattern, human exposure levels, environmental occurrence and toxiocological data) to share with the NTP on any of these chemicals, should contact Dr. William Eastin within 60 days of the appearance of this announcement. The information provided will be considered by the NTP in designing these studies.

Contact may be made by mail to: Dr. William Eastin, NIEHS/NTP, P.O. Box 12233, Research Triangle Park, North Carolina 27709, by telephone at 919–541–7941, fax 919–541–4714, or email at Eastin@NIEHS.NIH.GOV.

Dated: January 17, 1995.

Kenneth Olden,

Director, National Toxicology Program.

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BILLING CODE 4140–01–M

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[OR–094–6334–04: GP5–059]

Establishment of Supplementary Rules; Lane County, OR

AGENCY: Bureau of Land Management, Interior.

ACTION: Notice of establishment of supplementary rules.