MEMORANDUM

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SUBJECT: A One Month Anticoagulant Antidote Study in Beagle Dog
FINAL REPORT

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Sponsor: ICI Americas Inc.
Wilmington, Delaware 19897

Method:

Vitamin K1 was administered to beagle dogs, 2/sex/group at 2.0 mg/kg following a single oral dose of anticoagulant of either Brodifacoum (1.0 mg/kg) or Warfarin (300 mg/kg). One male and one female received Vitamin K1 6 hours after a single oral dose of anticoagulant on day 1, then twice daily for 4 days and then once daily for 3 days following. The other dogs received the antidote 24 hours after the anticoagulant (day 2), a second injection 31 hours after the anticoagulant (day 2), then twice daily for 3 days and then once daily for the next 3 days. Prothrombin and partial thromboplastin times were determined twice pretest and then only once on day 30. Body weights, food consumption were monitored. All survivors were sacrificed on day 31 followed by gross post mortem examinations. All tissues were then discarded.
Results:

There would appear to be no significant differences between prothrombin and partial thromboplastin times between the two pre-test periods and at the final 30 day post treatment period.

Conclusions:

These data would infer that Vitamin K1 is effective (i.m.) in the restoration of prothrombin and partial thromboplastin times after a single oral dose of either warfarin (300 mg/kg) or of Brodifacoum (1.0 mg/kg).

Validation:

This study is invalid. No test control animals were used to demonstrate the actual existence of blood coagulation problems that might be imposed by one single oral dose of either of the two anticoagulants administered orally. Prothrombin and partial thromboplastin times may indeed have returned to normal thirty day after the single oral administration of anticoagulant. There is no evidence that one single oral dose was effective in producing an anticoagulant effect. This study design is therefore considered to be invalid.

Attachments
ous epithelium. In the female the ovaries do not appear to be injured, fertilization of the ovum occurs, and gestation commences, but about the eighth day in the rat pathological changes develop in the placenta and the fetus dies and is absorbed. In addition to its effect on the reproductive function, vitamin E is a necessary factor for the preservation of the integrity of skeletal muscle. When female mice are maintained on a vitamin E low diet but are given a single dose of vitamin to ensure the birth of living young, the offspring show marked necrosis of skeletal muscle in 20 per cent of cases with early calcification (Pappenheimer).

VITAMIN K

Physiology.—This, the fourth of the fat-soluble vitamins, is of very much greater clinical significance than vitamin E on account of its relationship to bleeding. In 1930 Dam, of Copenhagen, noticed that chicks fed on a deficient diet developed hemorrhages owing to the loss of coagulating power of the blood, and that this was prevented by giving alfalfa. The coagulation factor in the alfalfa was extracted, crystallized and finally synthesized. It was called Kougulations-vitamin or vitamin K. The vitamin is necessary for the manufacture of prothrombin, so that when the vitamin is deficient the prothrombin in the blood is low, a condition of hypoprothrombinemia. Estimation of the plasma prothrombin thus affords a simple method of determining if there is a deficiency of vitamin K. Such deficiency in man is probably never due to lack of the vitamin in the food. In addition to the supply in the food, the vitamin is also manufactured by the normal bacteria of the bowel. As we have already seen in the case of fat-soluble vitamins A and D, it is a conditioned deficiency rather than a deficient supply of the vitamin which is the threat.

Pathology.—The three groups of conditions which may bring about vitamin K deficiency are: (1) biliary obstruction; (2) malabsorption of fat in celiac disease, pancreatic disease, sprue, hypermotility of the bowel, etc.; (3) failure of bacterial synthesis of the vitamin due to the action of antibiotics. The two major clinical conditions in which there is a dangerous degree of vitamin K deficiency are obstructive jaundice and hemorrhagic disease of the newborn. Unless bile is present in the bowel vitamin K is not absorbed, prothrombin is not formed in sufficient amount, and hemorrhage occurs. In obstructive jaundice bile is prevented from entering the bowel. This explains the marked tendency to bleeding after operations on jaundiced patients. The bleeding can be prevented by the administration of bile and vitamin K, or by giving the synthetic vitamin by mouth (the synthetic product is absorbed without the assistance of bile), or intravenously. If the liver is severely damaged (cirrhosis, amyloid, etc.) the administration of vitamin K is of no avail, because it is in the liver that the prothrombin is produced which is essential to coagulation. The explanation of bleeding in the newborn is that vitamin K is produced by the action of intestinal bacteria, and these are absent during the first few days of life. A contributing factor is the failure of the liver to produce bile during this period. At birth the baby has sufficient prothrombin from the maternal blood, but this rapidly falls, and there may be severe and even fatal hemorrhage, particularly intracranial. This is now prevented by giving the mother vitamin K before delivery. Bleeding due to vitamin K deficiency is of particular importance following operations for the relief of obstructive jaundice. In addition to bleeding from severed vessels, there may be hemorrhages in the skin and mucous membranes, particularly that of the bowel.

VITAMIN C. ASCORBIC ACID

We come now to the water-soluble vitamins, namely vitamin C and the B complex. Being soluble in water they are rapidly and readily absorbed from the small intestine, but for the same reason they are largely removed from food by the ordinary methods of cooking. The vitamin deficiency will therefore be of the primary type due to lack of the vitamin in the food, and not secondary to or conditioned by loss of power of absorption or storage of the vitamin.
Product Information

DICUMAROL
Capsules, USP

Description: Chemically, dicumarol is bis-(3,3'-methylenedioxy)benzhydrol. Its structural formula is: C_{16}H_{16}O_{5}.

Actions: Dicumarol reduces the concentration of prothrombin in blood and increases the prothrombin time by inhibiting the formation of prothrombin in the liver. Since the drug interferes with the production of prothrombin, the level of Factor II, IX, and X, their concentration in the blood is lowered during therapy. The inhibition of prothrombin involves interference with the action of vitamin K, and it has been postulated that dicumarol complexes with vitamin K for an enzyme essential to prothrombin synthesis.

After oral administration of dicumarol, maximum plasma concentrations are reached in two to eight hours. Greatest effect on prothrombin time is achieved in three to seven hours. After a single therapeutic dose of the drug, its effect on prothrombin time persists for four to five days.

Indications: Dicumarol is indicated for the prophylaxis and treatment of pulmonary embolism and of venous thrombosis and its extension, for therapy of atrial fibrillation with embolization, and as an adjunct in the treatment of coronary artery disease.

Contraindications: Dicumarol is contraindicated in patients who have active bleeding or subacute bacterial endocarditis.

Dicumarol is a potent drug, and its effects tend to be cumulative and prolonged. Caution should be used when dicumarol is administered in any situation in which the risk of hemorrhage is present. The drug should be withdrawn at the earliest sign of bleeding. It cannot be administered in a highly individualized and variable dose. Dose can be controlled only by periodic determination of prothrombin time. Clotting and bleeding times are not effective measures of control of therapy.

It is important to bear in mind that heparin sodium prolongs prothrombin time. Accordingly, when heparin sodium is given with dicumarol, a period of four to five hours after the last intravenous heparin injection and 12 to 24 hours after the last subcutaneous dose of heparin sodium should elapse before blood is drawn if a valid prothrombin time is to be obtained.

During pregnancy, both mother and fetus are subject to the risks of anticoagulant therapy with dicumarol; fetal hemorrhage and intrauterine death have occurred. Pregnant women should not be candidates for anticoagulant therapy with dicumarol and should be carefully evaluated and the indication critically reviewed. The withholding of the drug should be weighed against the possible dangers entailed in administering it. Since the drug is administered in the mother, the nursing infant should be observed for evidence of unexplained bleeding.

Precautions: Several factors influence the activity of dicumarol (and all Factors Influencing Activity of Dicumarol: any change in the intake of vitamin K, fat, or leafy green vegetables; vitamin K deficiency; vitamin C deficiency; x-ray therapy; and diarrhea, which causes increased loss in the stool and/or decreased absorption from the gastrointestinal tract. Many drugs can increase or decrease the effect of dicumarol on the prothrombin time. No other agent should be administered with dicumarol unless its potentialities for interacting with an oral anticoagulant are fully appreciated. If a drug is added or discontinued from a therapeutic regimen, it is essential that his prothrombin time be carefully monitored. Fatalities have been reported from interactions that affected the metabolism of coumarin anticoagulants or their binding to plasma proteins.

Care in patient selection is desirable to assure cooperation, particularly from alcoholic, emotionally unstable, psychotic, or senile patients. Bleeding during oral anticoagulant therapy may not always correlate with the prothrombin time.

Factors Influencing Activity of Dicumarol: Factors which enhance the anticoagulant action of dicumarol include decreased dietary intake or absorption of vitamin K, infection, cachexia, liver impairment, renal insufficiency, fever, malnutrition, sulfonamides, chloramphenicol, tetra-cycline, neomycin, or possibly other antibiotics.

Continued on next page
If prothrombin activity falls below the therapeutic range or if hemorrhage occurs, dicumarol should be temporarily withdrawn. If warranted by the clinical situation, phytomenadione (vitamin K) may be administered by slow intravenous injection in doses of 5 mg. in cases of mild overdosage and 20 to 40 mg. in cases of severe overdosage. Such use of vitamin K complicates subsequent anticoagulant therapy; therefore caution must be used in determining the need for this vitamin. It has been reported that a hypercoagulable state occurs following the rapid reversal of a prolonged prothrombin time.

How Supplied: B: Pulvule* Dicumarol, Capsules USP No. 314, 0.25 mg. (No. 4), Clear and No. 291, F.S., 50 mg. (No. 3, Clear), in bottles of 100 and 1,000.

** DICUMARIN PROCaine (merethoxylkynic acid) **

** Description:** Dicumarin * Procaine (merethoxylkynic acid) is an organic mercurial combined with procaine and theophylline for stabilization of the solution. Each mL contains—

2 N-o-Cr-Hydroxy-mucryl-2-methoxo-ethoxy- propyl-carbonate as mercuric chloride, as the Procaine Salt of the Anhydrase Acid 100 mg. (Equivalent to 39.3 mg. mercury and 45 mg. procaine base).

Theophylline, Anhydrous 50 mg. Contains 0.5 per cent chlorobutanol chloform derivative as a preservative. Sodium hydroxide and/or hydrochloric acid may have been added during manufacture to adjust the pH.

Prolonged exposure to direct sunlight should be avoided, since it causes darkening of the solution. Freqency is harmless. Refrigeration storage is recommended.

** Actions:** Like other mercurial diuretics, Dicumarin * Procaine (merethoxylkynic acid) inhibits the tubular reabsorption of sodium and chloride and, secondarily, water.

Mercurial diuretics have a dual action on potassium secretion. Urinary potassium is increased or decreased, depending upon whether the initial secretory rate is low or high. In the treatment of edema, mercurial diuretics usually increase potassium secretion slightly. For this reason, occasional potassium supplements are advisable.

** Indications:** Dicumarin * Procaine (merethoxylkynic acid) is indicated for the treatment of edema secondary to congestive heart failure, in the nephritic syndrome, the nephrogenic stage of glycosaminuria, and hepatic cirrhosis or portal obstruction.

** Contraindications:** Dicumarin * Procaine (merethoxylkynic acid) is contraindicated for intravenous use.

** Side Effects**:

- Should not be used when the patient is hypersensitive to mercury, procaine, or theophylline.
- In addition, because of the possibility of cross-sensitization, Dicumarin * Procaine should not be administered to patients who are sensitive to other drugs containing the paminobenzotiazole group, such as isoniazid, isocumarin, isozamide, etc. It is also contraindicated in patients with acute glomerulonephritis, ulcerative colitis, or gouty diathesis.

** Warnings:** A few instances of anaphylactic reactions have been reported. Use in Pregnancy: Since the safety of this preparation in pregnancy, during lactation, or in women of childbearing age has not been established, the drug should be used with caution in pregnant or lactating women.

** Precautions:** Diuresis of any kind should be induced with great caution in the presence of benign prostatic hypertrophy. Inhibition of kidney function by diuretics may precipitate obstruction if the blood urea nitrogen is more than 60 mg. per 100 ml. Mercurial diuretics should be used with caution if jaundice, risk of renal damage, or dosage increase is attempted.

** Lack of the antiprerenal, antitubular, and secondar y effects of thiazides, the use of mercurials for the treatment of renal disease is not indicated.**

** Bone marrow depression and neurologic toxicity do not occur.**

** Local reactions—** Gastrointestinal toxicity is rare. Hypersensitivity reactions—urticaria, rash, and angioedema do not occur. Excessive use of mercurial diuretics may cause impaired bone mineralization and proteinuria.

** Administration and Dosage:** Dicumarol is given by mouth. The dosage must be individualized and adjusted according to the prothrombin time. Probably the best method of reporting is prothrombin time is to give the patient's prothrombin time together with that of the control, both expressed in seconds. Many laboratories still report prothrombin time in percent of normal, on the basis of a prothrombin dilution curve; if this is done, it is essential for the laboratory to state what type of diluent was used.

There is no general agreement as to the minimum prothrombin time that accomplishes effective anticoagulation. The following schedule serves only as a guide. On the average, the dose for the first day in adults should be 150 to 200 mg. On subsequent days, the dose may range from 25 to 200 mg. When expressed in seconds, the prothrombin time should be maintained at one and one-half times the control value; this ratio varies with the different types of tissue thromboplastin used in performing the prothrombin time test.

Combined Use with Heparin—Because dicumarol has a slow onset of action, heparin should be used when a rapid anticoagulant effect is desirable. Both drugs can be given together at the start of therapy, and heparin administration may be continued for another four to seven days or until a satisfactory effect from dicumarol is obtained as determined by prothrombin time studies.

Management of Overdosage: Usually, an overly prolonged prothrombin time or minor hemorrhage will respond satisfactorily to withdrawal of the drug alone, but whole-blood transfusion may also be desirable in some cases.
Hymexazol
BP: Sankyo Co., Ltd. (Japan) (F-319)

Tack Trap * — see Sticky Trapping Materials.

Taenicidic
An anthelmintic intended especially for the control of
tapeworms (Taenia species).

Tag * — see PMA.

Tako * — see Dusts, Kaolin.

Talan * — see Dinobuten.

Talbot * — see Lead Arsenate.

Talc
CHEMICAL NAME: Hydrous magnesium silicate: Mg
(SiO₂·nH₂O).
APPLICATION: Inert carrier and diluent in pesticides.
When the ultra fine grinds are used (Mistron grades), they
contribute to large surface areas and are non-reactive with
sensitive toxicants and can be used in wettable powders.

BP: Cyprus Industrial Minerals Co., Talc Div.

Talcord *
CHEMICAL NAME: 3-phenoxylbenzyl 2,4, 2-dichlorovin-
yl0-4,3-dimethyl cyclopropene-1-carboxylate.
COMMON NAME: permethrin.

ACTION: Insecticide.

CHEMICAL PROPERTIES: More stable in acidic than in
alkaline solution. Moderately soluble in a range of
organic solvents. High thermal stability. Brown semi-solid
mass. Relatively non-volatile.

TOXICITY: Acute oral LD₅₀ to rats ranges from 430 mg kg
(male) to 470 mg kg (female); acute dermal LD₅₀ to rats
(undiluted material) > 2500 mg kg.

APPLICATION: Used for control of insects in a wide range
of crops. Also used for control of nuisance flies in animal
health.

FORMULATION: Emulsifiable concentrate.

BP: Shell International Chemical Co. (Great Britain)

Talon Rodenticide
CHEMICAL NAME: 3-[3-[3-3]-bromo-1-1 biphenyl]-4-xyl-1,
2, 3, 4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzozy-
pyran-2-one.

BP: Basic Producer, F: Formulator.

* Indicates trade name. BP: Basic Producer, F: Formulator.
* Indicates common name officially designated by USDA.
SLN: Special Local Need
Talon® Rodenticide (Cont.)

COMMON NAME: brodifacoum.
OTHER NAMES: PP581, WBA8119.
ACTION: anticoagulant rodenticide.
CHEMICAL PROPERTIES: Off-white powder. Soluble in benzene + chloroform, insoluble in water and petroleum ether. Stable as a solid under normal storage conditions.
TOXICITY: Acute oral LD₅₀ (rat), 0.27 mg/kg. Acute dermal (dust) LD₅₀ (rat), 30 mg/kg.
ANTIDOTE: Vitamin K₃.
HANDLING AND STORAGE PRECAUTIONS: Keep away from children, domestic animals and wildlife. Wash hands after handling bait. Do not allow to contaminate food, feed or water supplies. After treatment, remove and bury unedible bait and rodent bodies. Keep container closed to maintain freshness of bait. Do not re-use empty container.
APPLICATIONS: A new rodenticide of exceptional activity against a variety of pest rodents. Effective against rodents which are resistant to conventional anticoagulants. Simple feeding only necessary for rodent death to occur.
FORMULATIONS: Ready-to-use granule bait containing 50 ppm Talon® rodenticide in form of pellets (loose or pre-paks).

BP: ICI Americas Inc., Agricultural Chemicals Div., ICI Plant Protection Div. (Great Britain)

Tamaron — see Monitor.*

Tanol®
ACTION: A series of surfactants for formulation of wettability powders.
BP: BASF India Limited.

Tanalith® — see Wolman Salts*; Fluor Chrome Arsenate Phenol.

Tandex® (Product discontinued by FMC Corp., Agricultural Div.)
CHEMICAL NAME: m-C3,3-Dimethylureidophenyl-tert-butylocarboxamide.
COMMON NAME: karbutilate.
OTHER NAMES: MIA 11092, FMC 11092.
ACTION: Broad spectrum weed and brush killer for use on noncropland.
CHEMICAL PROPERTIES: White crystalline solid, melting at 170-175°C. Water solubility, 325 ppm at room temperature.
TOXICITY: Acute oral LD₂₀ (rat), 3000 mg/kg (tech. material in propylene glycol suspension).

SIGNAL WORD: CAUTION
CAUTION: Do not apply, or allow water to run near desirable trees or other crop plantings. Chemical may be washed off or absorbed by roots. Care should be taken to prevent spray to desirable plants. Tank mix and once the spray has been applied, vaporization exists.
APPLICATIONS: Control of annual weeds, grasses, brush, aquatic plants, utility and pipeline rights-of-way, industrial plant sites and noncropland.
FORMULATIONS: Granules, 10-20%

Tank Mix
A tank mix is a mixture of two or more active ingredients with the active ingredient clear by EPA requiring a new or a modified label. If such a mixture should be used with caution until compatibility of the ingredients is established.
The application of soluble concentrate alone or used alone as a spray there is no toxicity to insects in the tank, but when mixed with water, it is more toxic to insects in the tank. An undesirable chemical reaction occurs in the tank.
See Adjuxt, Serial Application.

Tanone® — see Phenolote.

Tantison®
CHEMICAL NAME: tert-butyl 4-tert-butyldimethyl-1,2,4-triazin-5-(4H)one.
COMMON NAME: Isomethiocynote.
OTHER NAME: DIC 1577.
ACTION: Herbicide.
CHEMICAL PROPERTIES: Colorless, odorless, white crystalline solid, m.p. 150.5°C, v.p. 3.3 x 10⁻¹ mm, insoluble in water. Solubility in hexane: 10.3%.
TOXICITY: Acute oral LD₂₀ (rat), > 1000 mg/kg.
APPLICATIONS: Used for control of grasses and weeds in winter barley; in combination with spring barley and spring wheat.
FORMULATIONS: Wettability powder + combination products with 2,4-DP (IFW).
Warfarin * — see Famphur *.

Warfarin *
CHEMICAL NAME: (3α-Acetonylbenzyl)-4-hydroxycoumarin.
COMMON NAMES: warfarin (BSI, ISO); coumafene (France), zoocoumarin (Netherlands and USSR).
ACTION: Rodenticide (anticoagulant).
TOXICITY: There has been no development of tolerance in rodents after ingestion and apparently neither sex nor age of the rat or mouse causes any difference in effectiveness.
SIGNAL WORD: WARNING - CAUTION.
APPLICATIONS: An anticoagulant that is highly effective in controlling Norway rats and house mice. It is odorless and tasteless and effective in very low dosages. Action is not rapid, usually about a week is required before a marked reduction in the rodent population is effected.
Warfarin has found very ready acceptance because rodents do not tend to become bait shy after once tasting the material. They continue to consume it until its anti-clotting properties have produced death through internal hemorrhaging.
A "rodent drink" is made with water containing 0.54; warfarin sodium coated on sugar (Dexthon * Water Soluble); a similar "rodent drink" containing 0.54% warfarin coated on sand (silica) (Rax * Water Soluble).
FORMULATION: It is formulated in ready-to-use baits and as concentrates in corn starch for mixing at a 1:1 ratio with cornmeal or other materials. Baits should be used only in protected stations that prevent access to larger animals. RAX powder, 30% concentrate.

WBA 8107 — see Ratak.  
WBA 8119 — see Talon *.
Weecon * — see Sodium Cyanate.
Weed The AAPCO has adopted this definition: "Any plant which grows where not wanted.
Weed-Ag-Bar * — see 2,4-D.
Weedar * — see 2,4-D; 2,4,5-T; MCPA.
Weedazol * — see Amitrole *.
Weedazol TL * — see Aziprole *.
Weedbeads * — see Sodium Pentachlorophenate.
Weed-B-Gon * — see 2,4-D, Silvex.
Weed Broom * (Product discontinued by manufacturer.)
COMPOSITION: DSMA, Bromacil and TCA.
ACTION: Herbicide.
APPLICATION: Industrial weed control.
Weed-E-Rad * — see DSMA, MSMA.
Weed-E-Rad * DMA Powder — see DSMA.
Weed-E-Rad * 360 — see DSMA.
Weedez Wonder Bar * — see 2,4-D.
Weed-Hoe * — see DSMA; MSMA.
Weedmaster *
COMPOSITION: Dicamba 1 pound; DMSA 1 pound; 2,4-D 1 gallon, a registered pre-mix.
ACTION: Herbicide.
TOXICITY: Acute oral LD₅₀ DMA: 7.5 mg/kg; Acute oral LD₅₀ of the DMSA: 12.5 mg/kg.
SIGNAL WORD: CAUTION.
APPLICATION: For control of annual and perennial leaf and vines on pastures and rangeland and in farm buildings.
Weedmaster * is currently cleared for use in Arkansas, Louisiana, and Mississippi.
FORMULATION: Liquid.
F: Velscicel Chemical Corp.
Weedol * — see Diquat; Parquat.
Weedone * — see 2,4-D; 2,4,5-T; Dethane *
Weed-Rhap * — see 2,4-D; MCPA.
Weed Rhap 2,4-D 2-Ethyl Hexyl Ester *
Weedtrine *
COMBINATION: Cetrine * plus diquat
ACTION: Aquatic herbicide.
APPLICATION: Registered for control of aquatic weeds. May be sprayed on only in depths no greater than 3 ft., Florida.
Weedtrine-D *
COMPOSITION: 6,7-Dihydridopyridine
Pyrazidine dibromide.