CHEMICAL MANUFACTURERS ASSOCIATION

June 10, 1996

Via Federal Express

These same comments were submitted previously to NIOSH, but without the attached cover letter.
Jon Busch/CMA

Ms. Diane Manning
Education and Information Division
NIOSH
4676 Columbia Parkway
Mail Stop C-34
Cincinnati, Ohio 45226-1998

Re: Draft Criteria Document for a Recommended Standard: Occupational Exposures to Metalworking Fluids (Feb. 23, 1996)

Dear Ms. Manning:

The Alkanolamines Panel of the Chemical Manufacturers Association is pleased to submit the enclosed comments on *NIOSH's Draft Special NIOSH Hazard Review: Metalworking Fluids*, dated February 23, 1996 (*Criteria Document*). These comments address issues pertinent to the discussion of alkanolamines. The Panel consists of the four major manufacturers of alkanolamines: Union Carbide Corporation, The Dow Chemical Company, Occidental Chemical Corporation, and Huntsman Corporation.

The Panel urges NIOSH to revise the recommended exposure limit (REL) stated in the *Criteria Document*. The recommended REL is overly stringent, and, in any event, does not address the causes of potential risks resulting from metalworking fluids (MWFs). The Panel is concerned that the proposed REL will not affect or ameliorate potential risks. Additionally, the Panel is concerned that the *Criteria Document* inaccurately describes the potential risks in MWFs relating to the presence of alkanolamines. The Panel urges NIOSH to revise the *Criteria Document* accordingly as suggested in the enclosed comments.

Please direct any questions concerning these comments to Mr. Jonathon T. Busch, Manager of the Alkanolamines Panel, at (703) 741-5633.

Sincerely,

Langley A. Spurlock, Ph.D., CAE
Vice President, CHEMSTAR

Attachment

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BEFORE THE
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

COMMENTS OF THE CHEMICAL MANUFACTURERS ASSOCIATION ALKANOLAMINES PANEL ON CRITERIA FOR A RECOMMENDED STANDARD: OCCUPATIONAL EXPOSURES TO METALWORKING FLUIDS

Criteria for a Recommended Standard: Occupational Exposure to Metalworking Fluids (Feb. 23, 1996)	)

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EXECUTIVE SUMMARY

The Alkanolamines Panel of the Chemical Manufacturers Association (CMA) submits these comments on the National Institute for Occupational Safety and Health's (NIOSH) *Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids*, dated February 23, 1996 (*Criteria Document*). The Panel is comprised of the four United States producers of monoethanolamine (MEA), diethanolamine (DEA), and triethanolamine (TEA).

These comments address issues pertinent to the discussion of alkanolamines in the *Criteria Document*. The Panel urges NIOSH not to revise the recommended exposure limit (REL) for metalworking fluids (MWFs) in the manner set forth in the *Criteria Document*, as the proposed REL is overly stringent and does not address the MWF constituents and/or byproducts that pose potential risk. Because the REL proposed in the *Criteria Document* is not related to the causes of potential risk, it may well have no effect on that potential risk. The Panel thus urges NIOSH, before establishing a new REL, to identify the causes of potential risks, based on further study of hazardous constituents, degradation products, and metal fines of MWFs currently in use. The Panel further urges NIOSH not to rely on epidemiological and other data that do not reflect current formulations or conditions, and to identify cost effective engineering and personal protective equipment controls. Additionally, the Panel urges NIOSH to revise the *Criteria Document*'s discussion of ethanolamines and of nitrosamines to reflect current data, exposure levels, and regulatory controls.

The Panel looks forward to discussing these issues at the public meeting scheduled for June 13 and 14, 1996. The Panel would be pleased to provide additional information and/or to meet further with NIOSH staff, upon NIOSH's request.

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ATTACHMENTS

INTRODUCTION

The Alkanolamines Panel of the Chemical Manufacturers Association (CMA) submits these comments on the National Institute for Occupational Safety and Health's (NIOSH) *Criteria for a Recommended Standard: Occupational Exposure to Metalworking Fluids* (*Criteria Document*), dated February 23, 1996.[1/] The Panel is comprised of the four United States producers of monoethanolamine (MEA), diethanolamine (DEA), and triethanolamine (TEA).[2/]

MEA, DEA, and TEA are amino alcohols used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. Non-cosmetic applications of the alkanolamines include uses in the manufacture of emulsifiers and dispersing agents for textile specialties, agricultural chemicals, waxes, mineral and vegetable oils, paraffins, polishes, metalworking fluids (MWFs), petroleum emulsifiers, and cement additives. They are intermediates for resins, plasticizers, and rubber chemicals. They also are used as lubricants in the textile

1/ The *Criteria Document* requests that comments be submitted by May 31, 1996. As set forth in the letter appended as Attachment 1, Mr. Ralph Zumwalde of NIOSH agreed, in a telephone conversation with Lisa Campbell on May 24, 1996, that NIOSH would consider the Panel's comments submitted on June 7, 1996, as if they had been submitted on May 31, 1996. Ms. Brenda Boutin of NIOSH also confirmed with Ms. Campbell, on May 28, 1996, that NIOSH would so consider the Panel's comments.

2/ Member companies include The Dow Chemical Company, Union Carbide Corporation, Huntsman Corporation, and Occidental Chemical Corporation.

industry, as humectants and softening agents for hides, as alkalinizing agents and surfactants in pharmaceuticals, as absorbents for acid gases, and in organic syntheses.[3/]

These comments address issues pertinent to the discussion of alkanolamines in the *Criteria Document*. The Panel is vitally interested in ensuring that the *Criteria Document* accurately reflects the existing toxicological and epidemiology data on MEA, DEA, TEA, and other MWF components. These comments are not detailed, nor do they address all of the issues pertinent to the Panel's interests.

The Panel acknowledges the submission by the Independent Lubricant Manufacturers Association (ILMA), a trade association that represents MWF manufacturers, on the *Criteria Document*. The Panel urges NIOSH to review carefully the studies and other information presented in that submission. In general, the Panel agrees with comments submitted by ILMA, whose members are experts on MWFs and their application. The Panel offers below clarification on specific points raised in ILMA'S comments with respect to alkanolamines, about which the Panel has significant expertise.

3/ *See* Christian, M.S. (ed.) (1983). "Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine," *Fifth Report of the Cosmetic Ingredient Review Expert Panel. J. Am. Coll. Toxicol. - Special Issue* 2(7):183-235,

I. THE PANEL URGES NIOSH TO REVISE THE *CRITERIA DOCUMENT* GENERALLY TO REFLECT POTENTIAL HAZARDS AND RECOMMEND APPROPRIATE COST EFFECTIVE CONTROL MEASURES

As discussed in more detail below, there is limited information regarding the causal agents of effects reported among those exposed to MWFs. Further study to establish cause and effect relationships should be conducted before the recommended exposure limit (REL) is revised, to ensure that the revised REL addresses the worker health concerns. The Panel believes that existing data do not support the conclusion that the proposed REL, the implementation of which will impose considerable costs, will decrease to any significant extent, if at all, potential risks from exposure to MWFs.

A. The Proposed REL May Not Affect Potential Risks Because It Does Not Address Or Take Into Account The Diversity Of MWFs

The *Criteria Document* contains a REL for MWFs of 0.5 mg/m^3 total particulate, which is intended to address "adverse respiratory health effects." The Panel is concerned that this REL is highly conservative and more stringent than necessary. Moreover, and importantly, the REL may have little or no effect on reducing potential risks to MWFs. This is because of the diversity of MWFs, their constituents, their degradation products, and the metal fines resulting where they are applied, and because the REL is not tied to the cause of any potential risks of exposure to MWF

constituents and degradation products. In short, the REL does not address appropriately the potential risk of exposure to MWFs.

Indeed, typically, occupational exposure limits are established for discreet chemicals based on the toxicological properties (acute and chronic exposures) for given end-points of the chemical under evaluation, considering viable routes of exposure, availability for exposure, availability of appropriate exposure controls, and other safety factors. Once established, exposure is expected to be controlled at or below the established limit, *i.e.*, monitoring methods are established to detect the chemical's presence in the workplace, and appropriate exposure controls are established. These factors simply are not present for the REL set forth in the *Criteria Document*.

The Panel therefore urges NIOSH to revise the *Criteria Document* to establish a REL or RELs that address appropriately and cost effectively the potential risks associated with hazardous components and degradation products of MWFs in use. Such RELs must be based on sound science, relating any limit set to the potential risk of the hazardous component, or degradation product, to which it applies.

1. MWFs, Their Constituents, And Their Byproducts Are Diverse, And The Proposed REL Does Not Address Appropriately Potential Risks Based On This Fact

MWFs are composed of a wide variety of chemicals, which are categorized into four major fluid types -- straight, soluble, synthetic, and semi-synthetic. These categories represent literally thousands of varied chemical formulations and emulsions. In use, these chemical formulations undergo microbial and thermal degradation, generating additional chemical constituents, which, along with the original fluids, vary in concentration continuously throughout the work day. Also included in the MWF aerosols are metal fines from the various metalworking operations.

While the *Criteria Document* discusses at great length potential adverse health effects for MWF exposure in general, it contains little discussion of the chemical composition of MWFs currently in use. The *Criteria Document* discusses some hazardous ingredients in MWFs, and then concludes that ". . .with additional research, it may be possible to identify specific MWF formulations with substantially lower risks."[4/] This statement implies that -- as a result of their constituents -- the MWFs themselves are hazardous and the source of the adverse health effects discussed in the *Criteria Document*. Little consideration is given to degradation products or metal fines that may well be more hazardous

4/ *Criteria Document* at 190.

than the original fluids and, importantly, that would likely also exist in fluids of "substantially lower risks." Since each MWF component and degradation product has its own toxicity characteristics, each should be controlled by appropriate occupational exposure limits, if necessary. The REL established in the *Criteria Document*, because it does not address MWF components and degradation products -- or the diversity of the various MWFs -- may not affect at all potential risks due to hazardous constituents.

2. A REL Should Be Based On A Defined Cause Of Any Potential Adverse Health Effect

The rationale for the proposed REL stated in the *Criteria Document* is stated as asthma and acute airflow reductions.[5/] No specific causes of these effects are stated or explained, however. The Panel recommends that before a REL is established, NIOSH further study hazardous constituents, degradation products, and metal fines of the MWFs currently in use, to analyze the chemical and particulate composition of representative sample metalworking operations using the four types of fluids. Once the chemical and particulate constituents of MWF in use are defined, a more definitive relationship can be drawn between the constituents and their known adverse health effects. At that point, exposure controls should be established for those hazardous components, if

5/ *See Criteria Document* at Section 10.

they do not already exist, resulting in control to appropriate levels and improved worker health and safety.

The Panel emphasizes in this regard that potentially hazardous decomposition products should be further studied, in addition to potentially hazardous constituents. For example, while the *Criteria Document* discusses nitrosamines and endotoxins,[6/] it does not address other potentially hazardous byproducts, nor does it address the potential health impact of metal fines from metalworking operations.

Moreover, even where NIOSH does discuss potentially hazardous byproducts, such as endotoxins, it does not explain how the REL will address their potential risks. For example, endotoxins produced by Gram-negative bacteria have been shown to cause the type of acute airflow reductions which form the basis for the proposed lowered REL. Reducing the REL based on total particulate, however, may have little or no impact on the control of endotoxin levels. Thus, the Panel suggests that further research on the identification and control of endotoxins in MWFs would much better and more appropriately meet the *Criteria*

6/ The Panel notes in this regard that it supports controls on conditions that could lead to the generation of nitrosamines, as well as controls on nitrosamines levels, as discussed in the Panel's Nitrosamines Position Paper, which is appended as Attachment 2. As further discussed below, Panel members are committed to supplying nitrosamine-free products and educating end-users regarding the hazards of nitrosamines and the conditions in which they are produced.

Document's goals in reducing the asthma and acute airflow effects stated to be of concern than would the proposed REL.

In this regard, the Panel additionally urges NIOSH to define better its characterization of the respirable and non-respirable fractions of MWF aerosols, as doing so would provide a basis for conclusions regarding the true potentially hazardous components and routes of entry. For example, the epidemiological effects (cancer) reported from chronic exposure in the esophagus, stomach, colon, and rectum, are likely due to ingestion of MWFs, their degradation products, and metal fines, rather than as a result of systemic effects of skin and inhalation exposure to the original MWF. With respect to this issue, the Panel notes that the epidemiology studies referenced in the *Criteria Document* were conducted prior to the removal of specific constituents and/or contaminants that could be causal of the effects reported in the referenced study findings. Thus, while the studies referenced may raise potential concern with MWF exposure, they should not be the basis for conclusions about current MWF exposures, because they do not reflect current MWF formulations or practices.

B. The Panel Urges NIOSH To Revise The REL To Address Potential Exposures And Appropriate Control Mechanisms More Accurately

The Panel urges NIOSH to revise the REL to state more fully and accurately potential routes of exposure to MWFs,

effective control measures, and effective exposure monitoring methods. With regard to potential routes of exposure, the proposed REL addresses inhalation only, when the primary route of exposure to MWF is dermal contact.[7/] The Panel therefore urges NIOSH to revise the *Criteria Document* and its recommendations to reflect this fact. The Panel further suggests that NIOSH provide guidance on cost effective exposure control mechanisms that would assist in establishing an achievable occupational exposure limit.

With regard to effective exposure control mechanisms, the Panel urges NIOSH to evaluate and recommend measures that will achieve necessary protection at a reasonable cost. With respect to this issue, NIOSH should consider the guidelines to the management and control of MWFs developed by Organization Resources Counselors (ORC) and the American National Standard Institute (ANSI). This is especially important given the cost of implementing existing controls necessary to meet the 0.5 mg/m^3 REL stated in the *Criteria Document*. For example, the cost for one automobile manufacturer to implement the engineering controls necessary to meet the proposed REL of 0.5 mg/m^3 is estimated at $1.5 billion.[8/]

The *Criteria Document* gives only limited consideration to the use of personal protective equipment to avoid exposure. The

[7/] This fact is demonstrated by the calculations set forth in the discussion below concerning ethanolamines.

[8/] Nancy DeMarco, "NIOSH Urges Lower Fluid Mist Exposures," *Lubes 'n' Greases*, May 1996 at 41-43.

Panel urges NIOSH to define effective engineering controls and their cost, and to research further and define acceptable personal protective equipment before issuing the REL in final form. Effective, specialized personal protective equipment could be established at less cost than the estimated $1.5 billion that will be needed to implement engineering controls.

With regard to exposure monitoring, the Panel believes NIOSH should determine appropriate and cost effective monitoring techniques, once the causal potentially hazardous constituents are identified.

II. THE PANEL URGES NIOSH TO REVISE THE *CRITERIA DOCUMENT*'S DISCUSSION OF ALKANOLAMINES AND NITROSAMINES

A. Ethanolamines Are Present In MWFs Only In Very Low Concentrations And Thus Pose Very Little Exposure Potential

Contrary to statements in the *Criteria Document*,[9/] ethanolamines (MEA, DEA, and TEA) do not contribute to the adverse health effects in MWF applications at the low concentrations in which they are used when exposures are controlled to the current

9/ Section 5 of the *Criteria Document* lists TEA as a selected potentially hazardous chemical ingredient of MWFs, and provides general information regarding its use, and the use of other alkanolamines. This section further outlines findings of a recent life-time study of TEA in rats and mice conducted by the National Toxicology Program (NTP) and other similar studies.

REL of 5 mg/m^3. This is due to the low potential for exposure to ethanolamines as MWF components and the relatively low toxicity of ethanolamines.

The *Criteria Document* erroneously refers to a concentration of 10 percent ethanolamine (EA) in bulk MWF formulations. According to ILMA, bulk MWFs typically contain 2-3 percent MEA or DEA, or up to 25 percent TEA. For convenience, ILMA recommended using a 5 percent concentration of MEA or DEA in MWFs, or a 25 percent concentration of TEA, as an upper bound when calculating risk. Bulk MWFs are typically diluted to an end-use concentration of 10:1 with water, according to ILMA, resulting in a final concentration of 0.5 percent MEA or DEA, or 2.5 percent TEA.

Using a 0.5 percent concentration of MEA or DEA in MWF, an upper bound of potential dermal worker exposure to MEA or DEA is calculated to be 0.24 mg/kg. Similarly, using a 2.5 percent concentration of TEA in MWF, an upper bound of potential dermal worker exposure to TEA is calculated to be 1.2 mg/kg. These calculations are set forth below:

Ethanola-mine	Hand/ Forearm Skin Surface Area	Estimated Maximum Film Thickness	Specific Gravity	Fraction of EA In MWF	Body Weight	Absorp-tion Factor	Potential Exposure
MEA or DEA	2300 square centi-meters[10/]	0.00981 centi-meters[11/]	1 g/ml	0.005	78.1 kg = 1.5 mg/kg[12/]	16%[13/]	0.24 mg/kg
TEA	2300 square centi meters[10/]	0.00981 centi-meters[11/]	1 g/ml	0.025	78.1 kg = 7.5 mg/kg[12/]	16%[13/]	1.2 mg/kg

10/ The United States Environmental Agency (EPA) states this to be the skin surface area of hands and forearms. *See* EPA, *Exposure Factors Handbook*.

11/ This is a highly conservative value for the film thickness for ethanolamine on the skin and assumes full immersion without any removal. *See* EPA, *Methods for Assessing Exposure to Chemicals*.

12/ EPA states that median adult male weight is 78.1 kg. *See* EPA, *Exposure Factors Handbook*.

13/ The 16 percent absorption factor used for these calculations is conservatively based on the percentage of DEA absorbed via the skin as stated in Matthews and Jeffcoat (1991). The Panel notes, however, that a much lower value has been determined -- 5 percent or less -- by Wachter, J.M., *et al.* *See* Wachter, J.M., *et al.* (1995). "Diethanolamine: Pharmacokinetics in Sprague Dawley Rats Following Dermal or Intravenous Administration" (CMA).

Furthermore, *in vitro* studies conducted by Sun *et al.* have demonstrated a lower percent absorption by human skin than by rodent skin. *See* Sun, J.D., *et al.* (1996). "*In Vitro* Penetration of Monoethanolamine and Diethanolamine Using Excised Skin from Rats, Mice, Rabbits, and Humans." *J. Toxicol. - Cut. & Ocular Toxicol.* 15(2):131-146.

The Panel believes that existing data support the conclusion that the 16 percent absorption factor would be approximately the same for MEA and TEA and thus uses it for the calculations for MEA and TEA.

The Panel notes that with respect to the dermal absorption rate of 16 percent used in the calculations set forth above, recent *in vitro* studies by Sun *et al.* show the absorption rate to be even less.[14/]

The estimated aerosol inhalation exposure to MEA, DEA, and TEA via MWFs is considerably lower -- at 0.0032 mg/kg for MEA and DEA, and at 0.016 mg/kg for TEA -- based on the following calculations:

Ethanolamine	Current REL	Percentage of Ethanolamine in MWF	Daily Human Air Intake	Body Weight	Potential Exposure
MEA or DEA	5 mg/m^3	0.005	10 m^3	78.1 kg	= 0.0032 mg/kg
TEA	5 mg/m^3	0.025	10 m^3	78.1 kg	= 0.016 mg/kg

These calculations demonstrate the minimal potential for worker exposure to ethanolamines from MWFs via either the dermal or inhalation routes, because ethanolamines are a minor component of MWFs.

In addition, with respect to exposure, the Panel notes that alkanolamines do not tend to concentrate in MWFs. This is due in part to the continual addition of water to the MWF process.

14/ Sun, J.D., *et al.* (1996). "*In Vitro* Penetration of Monoethanolamine and Diethanolamine Using Excised Skin from Rats, Mice, Rabbits, and Humans." *J. Toxicol. - Cut. & Ocular Toxicol.* 15(2):131-146.

B. Toxicity Data On Ethanolamines Show That They Are Unlikely To Result In Adverse Health Effects At Concentration Levels Present In MWFs

Extensive research has been conducted on ethanolamines to define their relative toxicity. The Panel is submitting for publication in June 1996, and will forward to NIOSH upon its completion, under separate cover, a comprehensive review of available subacute, subchronic, and chronic toxicity data for MEA, DEA, and TEA. These data support the conclusion that exposure to ethanolamines at the concentrations anticipated in MWF applications is not likely to result in any adverse health effects.

Section 5 of the *Criteria Document* describes draft results reported by NTP from a life-time TEA study conducted on male and female Fischer 344 rats and B6C3F1 mice. The draft report concludes that male rats showed "equivocal evidence" of kidney cancer, "no evidence" of cancer in female rats, "equivocal evidence" of liver cancer in male mice, and "some evidence" of cancer in female mice. The draft report has not yet been issued in final form.

Indeed, the Panel has supported an independent examination of the NTP rat and mouse studies under the direction of Dr. Judith McGregor. As discussed in the materials that the Panel recently submitted to NTP, which are appended as Attachment 3, the

investigation resulted in several very significant findings, which are expected to alter the report's conclusions.

Specifically, an evaluation of the rat studies by Dr. James Swenberg showed no statistical increase in kidney tumor incidence when data on serial kidney sections, a more sensitive and thorough means of detecting tumors in this tissue than the standard sectioning method that NTP used, were considered. Further, tumor incidences were within historical control ranges for NTP studies in which serial sectioning was conducted. An evaluation by Dr. James G. Fox of the mouse study showed the presence of *Helicobacter hepaticus*, a bacterium reported to cause liver tumors in mice, in both males and females. This bacterium confounds any attempt to evaluate tumorigenic potential of TEA in this tissue. Based on these results, the Panel has urged NTP to revise its report to state that the male rat kidney data show no evidence of carcinogenic activity and that the presence of *Helicobacter hepaticus* makes the mouse study results inadequate for the evaluation of liver and gastrointestinal oncogenic effects.

The expected changes in the NTP TEA study report are consistent with other cancer bioassays on TEA, as well as mutagenicity studies, which were negative. These other studies, including a recent evaluation in a transgenic mouse study, are discussed in the toxicology review of MEA, DEA, and TEA that the Panel will soon forward, under separate cover, to NIOSH. The

problems with the draft NTP study results noted above, coupled with the negative results of other cancer bioassays on TEA and negative mutagenicity data, show clearly, based on a weight of evidence, that TEA is not genotoxic nor carcinogenic. In short, these data show that TEA poses no cancer threat to humans.

The Panel also believes that DEA does not pose a cancer threat to humans in MWF applications, based on the low potential exposure to DEA in MWFs and other data that indicate that DEA is noncarcinogenic.[15/] There is also overwhelming evidence that DEA is not mutagenic/genotoxic, and DEA was negative in a transgenic mouse assay, as discussed in the toxicology review that the Panel

15/ The Panel notes that NTP recently released draft pathological evaluations of life-time studies of DEA with Fischer 344 rats and B6C3F1 mice. According to the draft NTP report, exposed rats showed no evidence of liver or kidney cancer, while exposed mice showed an increased incidence of liver tumors in males and females, and an increase in kidney tumors in males only, relative to unexposed study mice. The NTP report is interim and preliminary in nature. No detailed data have been made available, nor have statistical evaluations been conducted. Further evaluation of this study is essential to interpret these data, and to reach any conclusions based upon the study. For example, it is essential to determine the presence or absence of *Helicobacter hepaticas* in the study mice. While the NTP interim report on DEA stated that *Helicobacter hepaticas* was not present in the study mice, NTP may not have utilized techniques recently developed by the Massachusetts Institute of Technology (MIT) to identify this bacteria specifically, when other techniques fail to do so. This and other potential issues with regard to the study are addressed in the Panel's position paper on the study, which is appended as Attachment 4. In any event, the NTP study mice received daily dermal doses throughout their lifetimes at dose levels much higher than would be anticipated in MWF applications, *i.e.*, 40, 80, 160 mg/kg/day relative to 0.24 mg/kg (taking into account the 16 percent absorption factor) in MWF.

will soon forward, under separate cover, to NIOSH. Epidemiology evaluation of manufacturing workers also showed no cancer correlation to ethanolamines, as discussed in the forthcoming toxicology review.

C. Effective Controls Exist Already To Address Potential Risks Based On The Formation Of Nitrosamines

It is well known that under certain conditions, as described in the *Criteria Document*, ethanolamines, particularly secondary amines, such as DEA, can generate nitrosamines -- principally N-nitrosodiethanolamine (NDELA). These conditions have been controlled by EPA's prohibition on the addition of nitrosating agents to MWFs[16/] and its regulation of other conditions that may result in the formation of nitrosamines,[17/] as well as its significant new use rule (SNUR) requirements for alkali metal nitrites intended for use in MWFs.[18/]

Section 6.1.1 of the *Criteria Document* indicates that NDELA contamination was identified "in half of new and used straight oil samples at a mean concentration of 0.9 ppm (range 0.14-3.0)." The Panel knows of no data showing nitrosamines or NDELA to be present in straight oils or demonstrating any

16/ *See* 40 C.F.R. Part 747; 49 Fed. Reg. 2762 (Jan. 23, 1984).

17/ *See* 40 C.F.R. § 747.115.

18/ 40 C.F.R. § 721.4740.

relationship of such nitrosamines or NDELA to alkanolamines. This is particularly so given the fact that straight oils do not contain alkanolamines. If it is true that straight oils do contain nitrosamines or NDELA, their source(s) must be something other than alkanolamines.

With regard generally to other statements in the *Criteria Document* relating to nitrosamines and NDELA, the Panel endorses and incorporates by reference that section of the comments submitted by ILMA on the *Criteria Document* addressing nitrosamines. The Panel disagrees, however, with certain statements in the ILMA comments, as follows:

- With regard to NDELA, existing data show that NDELA is a weak carcinogen, as discussed in the Panel's position paper on nitrosamines and alkanolamines, a copy of which is appended as Attachment 2. As discussed in the Panel's position paper, while it has caused cancer in animal studies, NDELA appears to be one of the least potent carcinogens of the nitrosamine family, and studies of worker populations that may have had NDELA exposure in the past do not indicate carcinogenic effects.[19/]

19/ These issues are also discussed in a document prepared by the European Chemical Industry Ecology & Toxicology Centre (ECETOC), which the Panel urges NIOSH to consider. *See* ECETOC, *Technical Report No. 41: Human Exposure to N-*
(continued...)

- The Panel also disagrees that for metal removal fluid concentrates, the sole determining factor in the level of nitrosamine formed is the amount of diethanolamine (DEA) present. As described in the *Criteria Document*, specific conditions must exist for the generation of nitrosamines to occur. These include the following factors, which are critical: the presence of a nitrosating agent; an acidic pH level; an elevated temperature of the fluid; and the time of contact between the amine(s) and nitrosating agent(s).[20/]

In addition, the Panel disagrees with the statement in the *Criteria Document* that "TEA could be readily nitrosated to form N-nitrosdiethanolamine (NDELA)." This statement is misleading in any document discussing MWFs, because TEA is not readily nitrosated, particularly under the alkaline conditions present in MWFs. In the study referenced in the *Criteria Document* for this statement, TEA was nitrosated only at acidic pH -- a condition wholly inapplicable to MWFs -- at 90°C, and after 16 hours (the only time examined). The Panel thus urges NIOSH to revise this statement in the *Criteria Document*.

19/ (...continued)
Nitrosamines, their Effects, and a Risk Assessment for N-Nitrosdiethanolamine in Personal Care Products (Aug. 1990). The Panel would be pleased to provide a copy of this document to NIOSH, upon its request.

20/ *See Criteria Document* at 139.

Likewise, the Panel urges NIOSH to revise the sentence on page 139 of the *Criteria Document*, which states that "[c]ertain biocides can dissociate to form nitrite ions, which may react with alkanolamines, such as the mono-, di-, and triethanolamines, to form nitrosamines." This statement is incorrect and misleading in referring to MEA and TEA, which do not react with the nitrosating agents at issue to form nitrosamines, particularly under the conditions present with MWFs.

The Panel also urges NIOSH to revise the reference to the Fan *et al.* study, which NIOSH states "reported 0.02% to 3% concentrations of NDELA contamination in several unused, synthetic MWFs containing the alkanolamines TEA or DEA and nitrites."[21/] The Panel urges NIOSH to revise this discussion to state clearly that the data at issue in the Fan *et al.* study were collected in the 1970s -- before stringent controls on nitrites in MWFs were implemented in the United States and Europe.

The Panel wishes to note with respect to the nitrosamines issues affecting MWFs that it and its members, as signatories to CMA's Responsible Care® program and as product stewards, are committed to addressing concerns about alkanolamines and potential nitrosamine formation. Panel members have worked diligently since the mid-1970s to address these concerns -- both through research and through actions intended to minimize the formation of

21/ *Criteria Document* at 139.

nitrosamines. These initiatives are discussed in the Panel's position paper on this issue, which is appended as Attachment 2.

CONCLUSION

For all the reasons stated, the Panel urges NIOSH to revise the *Criteria Document* as suggested herein. Specifically, the Panel urges NIOSH, before establishing a new REL, to identify the causes of potential risks, based on further study of hazardous constituents, degradation products, and metal fines of MWFs currently in use. The Panel further urges NIOSH not to rely on epidemiological and other data that do not reflect current formulations or conditions, and to identify cost effective engineering and personal protective equipment controls. Additionally, the Panel urges NIOSH to modify the sections on alkanolamines and nitrosamines in the manner set forth above. The Panel would be pleased to meet with NIOSH to discuss its concerns in greater detail.

Attachments

Attachment 1

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May 24, 1996

Via Facsimile

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RE: *Draft Criteria For A Recommended Standard -- Occupational Exposures to Metalworking Fluids*

Dear Mr. Zumwalde:

This letter confirms the understanding of the Alkanolamines Panel of the Chemical Manufacturers Association regarding the National Institute for Occupational Safety and Health's (NIOSH) consideration of its comments on the above-referenced document. Based on a conversation between you and Lisa Campbell on May 24, 1996, the Panel understands that NIOSH has agreed to consider the Panel's comments as if they were submitted on or before May 31, 1996, if the Panel submits those comments on or before June 7, 1996.

Thank you for your assistance in this matter. Please call if you have any questions.

Sincerely,

Lisa M Campbell

Lynn L. Bergeson
Lisa M. Campbell

09LT002_.301 [02]

Attachment # 2

Nitrosamines and Alkanolamines

Position Statement of the Alkanolamines Panel, Chemical Manufacturers Association, USA

Since the mid 1970's, there has been concern about the possible presence of nitrosamines in Alkanolamines and the formation of nitrosamines when products containing Alkanolamines are used. The producers of Alkanolamines have worked diligently since that time to address these concerns – both through research and through actions intended to minimize the formation of these often undesirable compounds. This position statement summarizes the current state of the Alkanolamine industry as we strive to supply accurate information on this issue.

Why is there concern about nitrosamines?

As Alkanolamines producers, we are most concerned with one nitrosamine – N-nitrosodiethanolamine (NDELA). While it does cause cancer in animal studies, NDELA appears to be one of the least potent carcinogens of the nitrosamine family. Studies of worker populations that may have had NDELA exposure in the past do not indicate carcinogenic effects. While reassuring, some studies still suggest that people can be exposed to low levels of NDELA through some exposure routes, making it imperative that all users of Alkanolamines understand how to prevent formation of NDELA.

How and When Are Nitrosamines Formed?

NDELA is primarily formed under conditions of moderate to high acidity and elevated temperatures, when diethanolamine (DEA), a secondary amine, is brought into contact with nitrosating agents such as nitrites, nitrous acid, or nitrogen oxides. The rate of reaction is slow and relates most directly to the concentrations of the DEA and the nitrosating agents in solution.
There have been studies documenting the formation of NDELA at other conditions (high pH, lower temperatures) but at extremely slow reaction rates. Because the optimal conditions for formation are those of acidity, and since DEA itself is highly basic, formation of NDELA in pure DEA is not a major pathway to nitrosamine formation. Producers of Alkanolamines take many steps to prevent NDELA formation by maintaining high purity Alkanolamines free of nitrosating agents. It is theoretically possible to form nitrosamine from both monoethanolamine (MEA) and triethanolamine (TEA), but the conditions for these reactions are so severe chemically, and the rates of reaction are so tremendously slow, that it is *extremely* unlikely that MEA or TEA would make any significant contribution to nitrosamine formation.
Residual DEA in either product would probably still be of most interest to users seeking to prevent NDELA formation.

Because of the facts about NDELA formation, it is imperative that users DO NOT use nitrosating agents in conjunction with Alkanolamines. While this seems broadly known, we feel it is vital to reinforce this with all users because analytical surveys by government agencies occasionally find small amounts of NDELA in end-use products. This may be occurring because of contact between Alkanolamines (added for desirable properties) and nitrosating agents (possibly added on-purpose or added inadvertently as contaminants in other materials).

What are Alkanolamines Producers committed to doing on this issue?

Alkanolamines, because of their highly desirable properties, will necessarily continue to be used in a wide variety of applications. Therefore, we are committed to the following actions to help assure safe use of our products:

- We seek to educate all users of our products about the formation of nitrosamines that can occur when DEA comes into contact with nitrosating agents such as nitrites, nitrous acids, or nitrogen oxides. In fact, we specifically warn users NOT to create conditions which can lead to the formation of NDELA.

- We are committed to supplying nitrosamine free products to customers.

- We encourage research to identify nitrosating agents which may be inadvertently added to the formulated products that sometimes indicate low-level concentrations of NDELA.

- We are committed to the safe use and handling of Alkanolamines products, and we will work cooperatively with those parties interested in resolving nitrosation issues where our products are involved.

For more information, please call your supplier of Alkanolamines or Jon Busch, Manager, CMA Alkanolamines Panel, 202-887-1189. Members of the CMA Alkanolamines Panel include: The Dow Chemical Company, Occidental Chemical Company, Huntsman Corporation, and Union Carbide Corporation.

Attachment # 3

CHEMICAL MANUFACTURERS ASSOCIATION

April 25, 1996

Via Federal Express

J.R. Bucher, Ph.D.
National Institute of
Environmental Health Sciences
National Toxicology Program
111 TW Alexander Drive
Research Triangle Park, North Carolina 27709

Re: *Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in F344/N Rats and B6C3F1 Mice (Dermal Studies)*

Dear Dr. Bucher:

The Alkanolamines Panel of the Chemical Manufacturers Association submits this letter to urge NTP to withdraw, and revise, its *Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in F344/N Rats and B6C3F1 Mice (Dermal Studies) (Technical Report)*. The Panel believes that the *Technical Report* contains conclusions that are inaccurate, based on the Panel's review of the results of Dr. Judith MacGregor's review and audit of the study findings. The Panel is comprised of the four United States producers of monoethanolamine (MEA), diethanolamine (DEA), and triethanolamine (TEA).[1/]

The Panel appreciates the opportunity that NTP provided, pursuant to the meeting of Panel and NTP representatives on March 31, 1995, for the Panel to evaluate the data underlying the *Technical Report* before NTP issues the report in final form. Based on Dr. MacGregor's review and audit, and as further discussed below, the Panel urges NTP to withdraw the *Technical Report*, and to revise it to: (1) designate the Toxicology and Carcinogenesis Study of Triethanolamine in B6C3F1 Mice as inadequate for

1/ Member companies include The Dow Chemical Company, Union Carbide Corporation, Huntsman Corporation, and Occidental Chemical Corporation.

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evaluation of liver and gastrointestinal oncogenic effects; (2) state that the male rat kidney data show "no evidence of carcinogenic activity;" and (3) make the additional changes noted below.

Mouse Study Liver Issues

Based on Dr. MacGregor's review and audit of the study findings, the Panel believes that the *Technical Report*'s discussion of the mouse study should be revised in the following manner:

1. **Designate the Toxicology and Carcinogenesis Study of Triethanolamine in B6C3F1 Mice as "inadequate" for evaluation of liver and gastrointestinal oncogenic effects:** *Helicobacter hepaticus* has been shown to be present in liver tumors in both male and female mice in the high dose groups in the study using definitive culture and PCR techniques.[2/] *Helicobacter hepaticus* has been associated with an increase in hepatitis, cell turnover, and liver tumors in mice and is thus a confounding factor in this study. It is not possible to determine the influence of any interactive effect of triethanolamine and *Helicobacter hepaticus*. More importantly, it is not the purpose of carcinogenicity assays to evaluate such effects. Therefore, the NTP designation of "inadequate" is appropriate. As the definition of the "inadequate" category states, the study cannot be interpreted as valid for showing either the presence or absence of liver oncogenic activity in mice.

2. **Correct the data and discussion of the Warthin Starry staining results:** Only 11 of the 16 male mouse livers were positive. One male mouse that had karyomegaly and oval cell hyperplasia did not have a positive Warthin Starry stain result.

2/ *See* James G. Fox, "Role of *Helicobacter Hepaticus* in Confounding Results of Triethanolamine Carcinogenesis Assay in Mice." (Mar. 29, 1996). A copy of Dr. Fox's report is appended as Attachment 1.

3. **Reference and discuss Dr. Fox's laboratory investigative approach and results, as set forth in the report cited in note 2 and appended hereto as Attachment 1.**

4. **Revise the discussion of *Helicobacter hepaticus*:** The discussion of *Helicobacter hepaticus* is incorrect and incomplete. The conclusions are based on an assumption that animals that do not have karyomegaly and oval cell hyperplasia in the liver are not infected. This is not correct and should be revised accordingly.

Rat Study Kidney Issues

Based on Dr. MacGregor's review, the Panel urges NTP to withdraw the *Technical Report* and make the following revisions to its discussion of the rat study:

1. **Change the designation of "equivocal" for the male rat kidney adenomas to a designation of "no evidence of carcinogenic activity:"** The small microscopic adenomas cannot be distinguished from severe hyperplasia in sections from male rat kidneys.[3/] None of the trend tests for kidney tumors, hyperplasia, or combined proliferative lesions from original, step, or total sections are positive. The step section results did not indicate any increase in kidney tumors or hyperplastic lesions. The step section results are statistically different from the results of original sections. For these reasons, the designation of "equivocal" is not consistent with conclusions from other NTP studies in which step sectioning was done on male rat kidneys. The Panel therefore urges NTP to change the designation to "no evidence of carcinogenic activity," which accurately reflects the study results.

3/ Judith A. MacGregor, Ph.D., DABT "An Assessment of NTP's Conclusion that Triethanolamine Causes an Equivocal Increase in Kidney Tumors in Male Fischer Rats" (Jan. 5, 1996). A copy of Dr. MacGregor's report is appended as Attachment 2.

2. **Include the individual animal data from the step section evaluations on male rat kidneys in the *Technical Report*:** This information should be presented in the same format as the data from the original section evaluations.

3. **Include a statement in the report recognizing that severe hyperplasia cannot be distinguished from, at the most extreme lesion, small microscopic adenomas:** This statement is in the Pathology Working Group's (PWG) report of September 23, 1993, but is not mentioned in the draft report.

4. **Enhance the statistical evaluation to include a comparison of the data from the original sections and the step sections:** Add discussion about the fact that the data from the original sections are statistically different from the step sections when comparing total adenomas and also when comparing the frequency of adenomas in the mid-dose group from the original and step sections.

5. **Develop criteria for designating a study as "equivocal" when step sections are evaluated:** The criteria being used for this purpose are not clear and do not appear to be consistent. Triethanolamine did not cause any increase in adenomas in step sections from male rat kidneys. The Eustis *et al.* (1994) paper[4/] provides evaluations of 13 NTP studies in which step sections were evaluated in male rat kidneys. Of the 3 cases where the results were designated as "equivocal," all caused a slightly higher number of tumors or hyperplasia in both the original and step section evaluations.

* * * * *

4/ Eustis S., Hailey J.R., Boorman G.A., and Haseman J.K. (1994). The Utility of Multiple-Section Sampling in the Histopathological Evaluation of the Kidney for Carcinogenicity Studies. *Toxicol. Pathol.* 22:457-472.

We appreciate your assistance and would be pleased to discuss further with you our concerns and conclusions. If you have any questions, please call me at (202) 887-1189.

Sincerely,

Jonathon T. Busch

Jonathon T. Busch
Manager, Alkanolamines Panel

Attachments
cc: Kenneth Olden, Ph.D.

James G. Fox, DVM
Professor and Director

Division
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March 29, 1996

Jon Busch, Manager, Alkanolamines Panel
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Busch:

Enclosed please find the final *H. hepaticus* triethanolamine carcinogenesis report. If you have any questions, please do not hesitate to contact me. With best regards.

Sincerely,

James G. Fox, DVM
Professor and Director

JGF/jr

March 29, 1996

Role of *Helicobacter hepaticus* in Confounding Results of Triethanolamine Carcinogenesis Assay in Mice.

James G. Fox, DVM
Professor and Director
Division of Comparative Medicine
Massachusetts Institute of Technology
Cambridge, MA

TRIETHANOLAMINE NTP CHRONIC MOUSE STUDY

Purpose: Determine if *H. hepaticus* confounded results of triethanolamine carcinogenesis assay.

In the NTP Chronic Dermal Study of Triethanolamine in the $B_6C_3F_1$ mouse, an organism compatible with *Helicobacter hepaticus* was identified in a few liver sections from male mice (Triethanolamine NTP draft report; Fox *et al*, 1994; Ward *et al*, 1994). The prevalence of infection however, was not fully evaluated. Single sections of liver on each animal were taken to evaluate histological changes using H&E stain. In many cases, the liver sections were taken to evaluate grossly appearing nodules for evidence of neoplasia. Warthin Starry stain was used on one liver section from 15 male and four female animals. Bacteria were identified in the livers of 11 males and no females. Since *H. hepaticus* has been associated with the presence of liver neoplasia in A/JCr mice and since liver neoplasia was increased in the highest treatment groups in both male and female animals, accurate assessment to determine the extent of *H. hepaticus* infection was necessary to draw appropriate conclusions about the toxicity of triethanolamine in this study (Fox *et al,* 1994; Ward *et al*, 1994). Also, the correlation of the presence of karyomegaly and oval cell hyperplasia with the presence of *H. hepaticus* was assessed.

An increase in liver adenomas in male mice was evident in the highest treatment group. Overall, 42/50 male mice treated with 2,000 mg/kg of TEA had liver tumors compared with 31/50 in the controls. A significant number (33) of male mice in the high treatment group did not show evidence of karyomegaly or oval cell hyperplasia in the single liver section that was evaluated. These two liver lesions had previously been correlated with the presence of *H. hepaticus* in infected livers of A/JCr male mice (Ward *et al* 1994). Because these mice did not have these lesions, it was concluded that the animals were not infected with *H. hepaticus*.

In addition, there was a marked increase in liver tumors in female mice treated with TEA. A total of 41/50 females dermally treated with 1000 mg/kg triethanolamine had liver tumors compared to 23/50 controls. None of the female animals were diagnosed as being infected with *H. hepaticus* because they did not have karyomegaly or bile duct hyperplasia, nor was *H. hepaticus* seen in the livers of the 4 mice evaluated by Warthin Starry stain.

METHODS

Liver samples: Frozen and formalin fixed mice liver specimens were initially selected from mice which had been previously diagnosed with *H. hepaticus* by Warthin Starry examination of liver specimens; two additional mouse livers were included because they were diagnosed as being *H. hepaticus* negative (Table 1). Fixed specimens consisted of tissues samples from each of 3 different liver lobes. Frozen tissues consisted of liver tumors, the only frozen material available. In the second phase of the study, additional livers from 25 female and 19 male $B_6C_3F_1$ mice, none of which were diagnosed as being *H. hepaticus* positive based on lack of having any karyomegaly or oval cell hyperplasia, were analyzed (Ward *et al* 1994 a,b). These represented all of the frozen liver samples available from the study in the high dose animals that did not have nonneoplastic liver lesions. The high dose group female mice were treated with 1000 mg/kg and the male mice were treated with 2000 mg/kg (Tables 2 & 3).

Histology. Liver which had been fixed in neutral bufered 10% formalin and processed by standard methods and embedded in paraffin, were sectioned at 5μm and stained with hematoxylin and eosin (H&E) and Warthin Starry stain. The liver tissues were examined for histological changes and presence of *H. hepaticus*.

***H. hepaticus* culture:** Methods to isolate *H. hepaticus* utilized procedures developed in our laboratory (Fox *et al* 1994; Foltz *et al* 1995). *H. hepaticus* were isolated from livers by streaking liver homogenates onto TVP (Trimethoprim sulfa, Vancomycin, Polymyxin)

blood agar plates (Remel Labs, Lenexa, Kans.) and incubating at 37°C under microanaerobic conditions (GasPak system; BBL Microbiology Systems, Cockeysville, MD). *Helicobacter hepaticus* were characterized by typical colony morphology, Gram stain reaction, and urease, catalase and oxidase activity as previously described (Foltz *et al* 1995; Fox *et al* 1994). Cultures were held for 3 weeks to verify negative status.

PCR: Analysis of frozen liver specimens or bacterial culture by PCR followed protocols previously described and published (Shames *et al* 1995). Briefly, DNA was extracted from frozen mouse liver tissue. Approximately 15 mg of tissue were homogenized to uniformity using a plastic, microcentrifuge adapted pestle. Tissue or bacterial culture were then processed using the Rapid Prep Genomic DNA kit as outlined by the manufacturer (Pharmacia Biotech, Piscataway, NJ). DNA pellets were dissolved in 100 µl ddH_2O. Forty µl of a 50% chelex 100 solution (Bio-Rad, Hercules, CA) were added. The samples were incubated at 56°C for 30 min and this procedure was followed by heating at 94°C for 10 min. The samples were centrifuged at 12,000 rpm for 5 min. The primer sequences chosen for PCR amplification recognized a region of the 16S rDNA specific for *H. hepaticus*. These two oglionucleotides, 5' GCA TTT GAA ACT GTT ACT CTG 3' AND 5' CTG TTT TCA AGC TCC CC 3', produced an amplified product of 417 bp. Twenty µl of the DNA preparation was added to 100 µl (final volume) reaction mixture containing 1 x Tth polymerase buffer (supplied by the manufacturer but supplemented with 1M $MgCl_2$ to a final concentration of 2. 75 mM), 0.5 µM each of the two primers, 200 µM each deoxynucleotide, and 200 µg of bovine serum albumin per ml. Samples were heated at 94°C for 4 min, briefly centrifuged, and cooled to 61°C. At this time, 3.2 U of Tth polymerase (Pharmacia) and 1.25 U of polymerase enhancer (Perfect Match, Stratagene, La Jolla, California) were added, followed by an overlay of 100 µl of mineral oil. The following conditions were used for amplification: denaturation at 94°C for 1 min, annealing at 61°C for 2 min and elongation at 72°C for 2 min. A total of 35 cycles were performed and were followed by an elongation step of 7 min at 72°C. A 10 to 15 µl aliquot of the sample was then electrophoresed through a 6% Visigel separation

matrix (Stratagene); this was followed by ethidium bromide staining and viewing by UV illumination.

Immunofluorescence staining of mouse livers: Livers from 19 male mice and from 25 female mice were processed for immunofluorescence staining using polyclonal *H. hepaticus* rabbit antisera. Tissue sections were deparaffinized and rehydrated through xylene and ethanol to water. The slides were incubated with 0.05% pronase (Sigma P5147) for 30 min at 37°C and washed with PBS for 5 min. The tissue sections were covered with either rabbit preimmune serum or postimmune serum to *H. hepaticus* whole cell sonicate extract (both 1:100 in PBS) and incubated for 60 min at 37°C in a humid atmosphere. Slides were then washed twice in PBS (5 min each time) incubated for 30 min with anti-rabbit IgG-fluorescein isothiocyanate conjugate (1:50 in PBS; Sigma F0511) at 37°C, and rinsed in PBS for 5 min. The slides were mounted with coverslips and sealed with buffered glycerol. Slides were examined with a Zeiss fluorescence microscope.

RESULTS

Histology: In the first phase of the study, organisms compatible with *H. hepaticus* were seen in 6 of the 7 mice analyzed (Table 1). Although a female mouse with adenoma in the liver did not have definite *H. hepaticus* observed, nor karyomegaly or oval cell hyperplasia, the liver was positive for *H. hepaticus* by culture and PCR.

In addition, evaluation of livers by H & E histology in the second phase of the study did not indicate presence of karyomegaly or oval cell hyperplasia in any sample analyzed (See Appendix I for individual pathologists' reports). Warthin Starry stain of liver specimens in the second phase of the study were analyzed by 2 boarded pathologists. There was poor correlation of results not only between the two pathologists but also with results obtained by culture, PCR, and FA (Tables 2 & 3).

***H. hepaticus* culture:** In the initial pilot study, all 5 mice were positive for *H. hepaticus* by culture. Organisms were Gram negative, motile and measured 1.5 to 5 μm long and 0.2 to 0.3 μm wide. The bacteria were oxidase, catalase, and strongly urease positive (Table 1).

Mouse liver tumor specimens from the additional mice surveyed were also positive by culture, but at a lower prevalence; 7/25 (28%) of the female mice had *H. hepaticus* recovered from their livers whereas 7/19 (36.8%) of the males livers were *H. hepaticus* positive by culture (Tables 2 & 3).

PCR: In the initial screen, DNA from all 5 *H. hepaticus* strains amplified a PCR product specific for *H. hepaticus* (Table 1). In the second phase of the study of the 25 female livers, 12 livers were positive for *H. hepaticus* specific PCR products for an overall evidence of 48%. Ten of 19 (52.6%) male livers had *H. hepaticus* specific DNA PCR products amplified (Tables 2 & 3).

Fluorescent Antibody Assay: The FA assay correlated with culture in 58% (14/25) of the female mice and 63% (16/19) of the male mice. Comparison of FA with PCR yielded comparable results, 68% (19/25) in females and 63% (12/19) in male mice.

DISCUSSION

Based on a combination of both culture and PCR analysis, *H. hepaticus* was identified in all frozen liver tumor samples from the initial survey and from a significant number, 12/25 (48%) and 10/19 (52.6%) in female and male $B_6C_3F_1$ mice respectively in the second phase of the study. The results of the study clearly demonstrate that even though the mice from the second phase did not have any karyomegaly or oval cell hyperplasia, they were infected with *H. hepaticus*. Additionally, the analysis was obtained on a single sample of oncogenic tissue which was not representative of the liver as a whole. The criteria relying solely on the presence of the histopathological features for a presumptive diagnosis of *H. hepaticus* are not reliable and should not be used as definitive indicators

of presence or absence of *H. hepaticus* in both female and male $B_6C_3F_1$. These features had been used previously as indicators of *H. hepaticus* infection in A/JCr male mice, but these evaluations were based on histological criteria only and were not verified by either culture or PCR testing (Ward *et al* 1994 a,b). Based on a longitudinal study of *H. hepaticus* in A/JCr mice, *H. hepaticus* efficiently colonizes the cecum and colon of virtually 100% of the mice on a persistent basis (Fox *et al* in press). Thus, it is likely that a high percentage of the $B_6C_3F_1$ mice were also persistently infected throughout the 2 year study.

An assessment of *H. hepaticus* infection in livers of 44 mice by several diagnostic methods - 1) Culture; 2) PCR; 3) Fluorescent labeled IgG *H. hepaticus* polyclonal antibody and 4) evaluation of livers for *H. hepaticus* by Warthin Starry stain indicated that a positive correlation of culture and PCR results occurred in 80% (20/25) and 84% (16/19) of female and male mice respectively. Reliability of the two other diagnostic assays varied and was not considered predictative of *H. hepaticus* infection in the livers examined. Comparing culture and PCR, with culture results of *H. hepaticus* serving as the gold standard, the sensitivity and specificity in female mice was 100% and 72% respectively. In male mice, the sensitivity was also 100% and the specificity was 75%. More detailed culture of several lobes of liver would most likely raise the specificity of the test.

Our culture and PCR data strongly supports the hypothesis that the hepatitis, including oval cell hyperplasia and hepatic karyomegaly, i.e. non neoplastic liver lesions in 18% to 34% of the male mice in all groups, including controls, was the result of *H. hepaticus* infection. This finding is consistent with earlier observations in A/JCr infected with *H. hepaticus* (Ward *et al* 1994; Fox *et al* in press). Furthermore, our findings of *H. hepaticus* in $B_6C_3F_1$ mice with and without these 'characteristic' nonneoplastic lesions indicate that the presence of *H. hepaticus* complicated interpretation of the relationship of triethanolamine with liver neoplasia in both male and female mice. In summary, one cannot conclude any evidence of carcinogenic activity of triethanolamine in either male

or female $B_6C_3F_1$ because of the confounding of *H. hepaticus* infection in the mice on this study.

Longitudinal studies recently completed in our laboratory indicate that BrdU labeling of hepatocytes is statistically higher in 10-13 month old A/JCr male and female *H. hepaticus* infected mice when compared to age matched A/J not infected with *H. hepaticus* (Fox *et al* in press). *H. hepaticus*, by causing proliferation of hepatocytes may have a promoting effect and enhance tumorigenesis by certain compounds. Potential mechanisms responsible for *H. hepaticus* pathogenesis and oncogenic potential, and interactions with chemicals targeting the liver require further study.

REFERENCES

Foltz CF, Fox JG, Yan L, Shames B. Evaluation of antibiotic therapies for eradication of *Helicobacter hepaticus*. Antimicrobial Agents Chemotherapy 39:1292-1294, 1995.

Fox JG, Dewhirst FE, Tully JG, Paster BJ, Yan L, Taylor NS, Collins MJ, Gorelick PL, Ward JM. *Helicobacter hepaticus* sp. nov, a microaerophilic bacterium isolated from livers and intestinal mucosal scrapings from mice. J Clin Micro 32:1238-1245, 1994.

Fox JG, Li X, Yan L, Cahill RJ, Hurley R, Lewis R and Murphy JC. Chronic proliferative hepatitis in A/JCr mice associated with persistent *H. hepaticus* infection: A model of Helicobacter induced carcinogenesis. Infect Immun (in press).

Shames B, Fox JG, Dewhirst FE, Yan L, Shen Z, Taylor NS. Identification of widespread *H. hepaticus* infection in feces in commercial mouse colonies by culture and PCR assay. J Clin Microbiol 33:2968-2972, 1995.

Ward J.M, Anver MR, Haines DC, and Benveniste RE. Chronic active hepatitis in mice caused by *Helicobacter hepaticus*. Am J Pathol 145:959-968, 1994.

Ward JM, Fox JG, Anver MR, Haines DC, George CV, Collins MJ Jr, Gorelick PL, Nagashima K, Gonda MA, Gilden RV, Tully JG, Russell RJ, Benveniste RE, Paster BJ, Dewhirst FE, Donovan JC, Anderson LM, Rice JM. Chronic active hepatitis and associated liver tumors in mice caused by a persistent bacterial infection with a novel *Helicobacter* species. J Nat Cancer Inst 86:1222-1227, 1994.

Table 1: *H. hepaticus* in $B_6C_3F_1$ mice, NTP Triethanolamine Study

181	Hm	++++	Adenoma	3/3	Chronic active	No tissue
210	Hm	+++	Carcinoma, adenoma	3/3	Chronic active	No tissue
217	Hm	++++	Multiple adenoma	2/3	Chronic active	Positive **
121	Mm	++++	Multiple carcinoma, multiple adenoma	2/3	Chronic active	Positive
32	Cm	+++	Carcinoma, multiple adenoma	2/2	Chronic active	Positive
246	Cf	+-	Adenoma	-/-	No significant lesions	Positive
31	Cm	+++	Multiple carcinoma, multiple adenoma	2/3	Chronic active	Positive

H=high, M=medium; C=control
m=male; f=female
(Hm=high dose male)
* Based on 3 different sections of liver tissue
** Positive in all 5 livers by culture and confirmed by PCR

TABLE 2

***H. hepaticus* in $C_6C_3F_1$ Mice, NTP Triethanolamine Study**

Females

		H. h **by Histology**		***H. h.*** **by fluorescent antibody**	***H. h.*** **by culture or PCR**	
ACC.#	**ID#**	**#1**	**#2**	**FA**	**C**	**PCR**
95-5449	421	-	-	+	+	+
95-5450	424	-	-	-	+	+
95-5451	425	-	-	-	-	+
95-5452	426	+	-	-	-	-
95-5453	429	-	-	-	-	-
95-5454	430	-	-	+	-	+
95-5455	431	+/-	-	-	-	-
95-5456	432	-	-	-	-	-
95-5457	437	-	-	-	-	-
95-5458	439	-	-	+	-	+
95-5459	440	-	-	-	-	-
95-5460	442	-	-	-	-	-
95-5461	443	+/-	-	+	-	-
95-5462	445	+/-	-	-	-	-
95-5463	449	+	-	-	-	-
95-5464	450	+	-	-	+	+
95-5465	451	+	-	+	-	-
95-5466	453	-	-	-	-	+
95-5467	459	+/-	-	-	+	+
95-5468	465	+/-	-	+	-	-
95-5469	466	-	-	-	+	+
95-5470	471	-	+	-	-	-
95-5471	472	-	-	+	+	+
95-5472	475	-	-	-	-	-
95-5473	477	+	-	+	+	+

#1 = Pathologist #1 - Presence or absence of *H. hepaticus* based on Warthin-Starry stain.
#2 = Pathologist #2 - Presence or absence of *H. hepaticus* based on Warthin-Starry stain.
FA = *H. hepaticus* fluorescent antibody assay.
C = Culture.
PCR = Polymerase chain reaction.

TABLE 3

H. hepaticus in $C_6C_3F_1$ Mice, NTP Triethanolamine Study

Males

		H. h by Histology		*H. h.* by fluorescent antibody	*H. h.* by culture or PCR	
ACC.#	ID#	#1	#2	FA	C	PCR
95-5474	185	-	-	-	-	-
95-5475	188	-	-	+	-	-
95-5476	190	-	-	+	-	-
95-5477	195	+	+	-	-	-
95-5478	197	+	-	+	-	+
95-5479	199	-	-	-	-	-
95-5480	200	-	-	+	+	+
95-5481	201	+	+	-	+	+
95-5482	203	+	+	+	+	+
95-5483	211	-	-	-	-	-
95-5484	212	+	-	+	-	-
95-5485	213	+	-	-	-	-
95-5486	215	-	+	+	+	+
95-5487	220	-	-	-	-	-
95-5488	224	+	-	-	+	+
95-5489	230	+	+	+	+	+
95-5490	232	+	-	-	-	+
95-5491	234	+	-	-	-	+
95-5492	235	+	+	+	+	+

#1 = Pathologist #1 - Presence or absence of *H. hepaticus* based on Warthin-Starry stain.
#2 = Pathologist #2 - Presence or absence of *H. hepaticus* based on Warthin-Starry stain.
FA = *H. hepaticus* fluorescent antibody assay.
C = Culture.
PCR = Polymerase chain reaction.

Appendix I

DCM RESEARCH
PATHOLOGY

Research#: CMA **Investigator:** Fox/Seely **Pathologist:** Li
Research Title: H. hepaticus in Batelle Mice **Date:** 12/26/95
Account Charge#: CMA **Prosector:** Batelle
Group#: 2

Species: Mice **Strain:** ? **Sex:** M/F **Age:** **Body Weight:**

Pertinent Information: Tissue cassette fixed in formalin sent to Dr. Fox. One cassette was submitted per animal, with two pieces of liver in each cassette. The animals were treated with triethanolamine.

Accession#	Sex	ID #	Frozen ID#	Triethanolamine	Gross Findings
95-5449	F	421	BC585	1000 mg/kg	No significant lesions.
95-5450	F	424	BC878	1000 mg/kg	No significant lesions.
95-5451	F	425	BC636	1000 mg/kg	No significant lesions.
95-5452	F	426	BC667	1000 mg/kg	No significant lesions.
95-5453	F	429	BC820	1000 mg/kg	No significant lesions.
95-5454	F	430	BC694	1000 mg/kg	No significant lesions.
95-5455	F	431	BC853	1000 mg/kg	No significant lesions.
95-5456	F	432	BC862	1000 mg/kg	No significant lesions.
95-5457	F	437	BC901	1000 mg/kg	No significant lesions.
95-5458	F	439	BC593	1000 mg/kg	No significant lesions.
95-5459	F	440	BC592	1000 mg/kg	No significant lesions.
95-5460	F	442	BC807	1000 mg/kg	No significant lesions.
95-5461	F	443	BC884	1000 mg/kg	No significant lesions.
95-5462	F	445	BC751	1000 mg/kg	No significant lesions.
95-5463	F	449	BC843	1000 mg/kg	No significant lesions.
95-5464	F	450	BC718	1000 mg/kg	Irregular capsular contours of both pieces.
95-5465	F	451	BC754	1000 mg/kg	No significant lesions.
95-5466	F	453	BC677	1000 mg/kg	No significant lesions.
95-5467	F	459	BC762	1000 mg/kg	No significant lesions.
95-5468	F	465	BC837	1000 mg/kg	No significant lesions.
95-5469	F	466	BC893	1000 mg/kg	No significant lesions.
95-5470	F	471	BC851	1000 mg/kg	No significant lesions.
95-5471	F	472	BC778	1000 mg/kg	No significant lesions.
95-5472	F	475	BC630	1000 mg/kg	No significant lesions.
95-5473	F	477	BC841	1000 mg/kg	One nodule in one, two in other lobes.
95-5474	M	185	BC844	2000 mg/kg	No significant lesions.
95-5475	M	188	BC698	2000 mg/kg	No significant lesions.
95-5476	M	190	BC640	2000 mg/kg	No significant lesions.
95-5477	M	195	BC629	2000 mg/kg	No significant lesions.
95-5478	M	197	BC587	2000 mg/kg	Irregular capsular contusion both lobes.
95-5479	M	199	BC726	2000 mg/kg	No significant lesions.
95-5480	M	200	BC705	2000 mg/kg	Irregular capsular contusion both lobes.
95-5481	M	201	BC731	2000 mg/kg	No significant lesions.
95-5482	M	203	BC846	2000 mg/kg	Nodule in one lobe.
95-5483	M	211	BC763	2000 mg/kg	No significant lesions.
95-5484	M	212	BC700	2000 mg/kg	No significant lesions.
95-5485	M	213	BC805	2000 mg/kg	No significant lesions.
95-5486	M	215	BC670	2000 mg/kg	No significant lesions.
95-5487	M	220	BC661	2000 mg/kg	No significant lesions.
95-5488	M	224	BC775	2000 mg/kg	No significant lesions.
95-5489	M	230	BC788	2000 mg/kg	No significant lesions.

R95-5449-5488

95-5490	M	232	BC749	2000 mg/kg	No significant lesions.
95-5491	M	234	BC639	2000 mg/kg	Irregular capsular contour in one lobe.
95-5492	M	235	BC716	2000 mg/kg	No significant lesions.

Histopathologic Observations:

95-5449
Liver: No significant lesions (a few tiny foci of mononuclear cell infiltration). Warthin-Starry stain revealed no *Helicobacters* in bile canaliculi.
95-5450
Liver: No significant lesions (a few tiny foci of mononuclear cell infiltration). Artifact in Warthin-Starry section makes it difficult to interpret the presence of organism.
95-5451
Liver: No significant lesions (a few tiny foci of mononuclear cell infiltration). Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5452
Liver: A clear cell focus in one lobe. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5453
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5454
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5455
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5456
Liver: Hepatocellular carcinoma with sinusoidal dilation filled with blood and hepatocyte hypertrophy in one lobe. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5457
Liver: Leukemia/lymphoma characterized by marked infiltration of lymphoid cells in both lobes. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5458
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5459
Liver: Focal hepatocyte hypertrophy. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5460
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5461
Liver: Minimal mononuclear cell infiltration in a few portal triads in one lobe. Hepatocytes appear to be hyperplastic in the other lobe (adenoma?). Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*
95-5462
Liver: Minimal mononulcear cell infiltration in a few portal areas and focal hepatocyte necrosis in one lobe. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*
95-5463
Liver: No significant lesions. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*
95-5464
Liver: Focal nodular hyperplasia in both lobes. No significant lesions. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*
95-5465
Liver: No significant lesions. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*
95-5466
Liver: Minimal to mild multifocal mononuclear cell infiltration in the parenchyma and portal triads (leukemia?). Warthin-Starry revealed no typical *Helicobacters* in canaliculi.
95-5467
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

R95-5449-5492

95-5468
Liver: A few tiny foci of hepatocyte degeneration and necrosis with mononuclear cell and neutrophil infiltration in the parenchyma. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5469
Liver: Two lymphocytic foci around the intralobular bile duct and vein. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5470
Liver: Minimal portal mononuclear cell infiltration. A few *H. hepaticus* like organisms seen on Warthin-Starry sections.

95-5471
Liver: Nodular hyperplasia/adenoma/carcinoma of hepatocytes in both lobes. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*

95-5472
Liver: Nodular hyperplasia and minimal mononuclear cell infiltration in a few portal areas. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5473
Liver: Hepatocyte adenoma/carcinoma and leukemia/lymphoma characterized by marked infiltration of lymphoid cells in both lobes. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5474
Liver: No significant lesions. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*

95-5475
Liver: Focal hypatocyte hyperplasia in one lobe. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*

95-5476
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5477
Liver: Minimal to mild portal inflammation of mononuclear cells. Numerous *H. hepaticus* like organisms seen in Warthin-Starry sections.

95-5478
Liver: Nodular hyperplasia/adenoma of hepatocytes. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5479
Liver: No significant lesions. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*

95-5480
Liver: Hepatocellular hyperplasia/adenoma/carcinoma in one lobe. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5481
Liver: No significant lesions. Many *H. hepaticus* like organisms seen in Warthin-Starry sections.

95-5482
Liver: Nodular hyperplasia/adenoma and mild periportal hepatitis. Numerous *H. hepaticus* like organisms seen in Warthin-Starry sections.

95-5483
Liver: Nodular hyperplasia. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5484
Liver: No significant lesions. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*

95-5485
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5486
Liver: No significant lesions. Many *H. hepaticus* like organisms seen on Warthin-Starry sections.

95-5487
Liver: No significant lesions. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5488
Liver: Focal hepatocyte hyperplasia. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*

R95-5449-5492

95-5489

Liver: Minimal to mild portal and parenchymal infiltration of mononuclear cells. Numerous *H. hepaticus* like organisms seen in Warthin-Starry sections.

95-5490

Liver: Minimal portal to parenchymal infiltration of mononuclear cells. Warthin-Starry revealed no typical *Helicobacters* in canaliculi.

95-5491

Liver: No significant lesions. Stain artifact in Warthin-Starry sections makes it difficult to evaluate the presence of *Helicobacters.*

95-5492

Liver: Mild multifocal necrotic hepatitis. Numerous *H. hepaticus* like organisms seen in Warthin-Starry sections.

(3/26/96)
Lab Requests:
( )Micro ( )Hema ( )Sero ( )Para ( )Urin ( )Clin Chem ( )Photos ( ) Specimen Frozen
TISSUE PRESERVATION: ( )Formalin ( )Other Fixative (specify)
( )Freeze -70°C (specify tissues)

DCM RESEARCH
PATHOLOGY

Research#: CMA **Investigator:** Fox/Seely **Pathologist:** Dangler
Research Title: H. hepaticus in Batelle Mice **Date:** 12/26/95
Account Charge#: CMA **Prosector:** Batelle
Group#: 2

Species: Mice **Strain:** ? **Sex:** M/F **Age:** **Body Weight:**

Pertinent Information: Tissue cassette fixed in formalin sent to Dr. Fox. One cassette was submitted per animal, with two pieces of liver in each cassette. The animals were treated with triethanolamine.

Accession#	Sex	ID #	Frozen ID#	Triethanolamine	Gross Findings
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95-5452	F	426	BC667	1000 mg/kg	No significant lesions.
95-5453	F	429	BC820	1000 mg/kg	No significant lesions.
95-5454	F	430	BC694	1000 mg/kg	No significant lesions.
95-5455	F	431	BC853	1000 mg/kg	No significant lesions.
95-5456	F	432	BC862	1000 mg/kg	No significant lesions.
95-5457	F	437	BC901	1000 mg/kg	No significant lesions.
95-5458	F	439	BC593	1000 mg/kg	No significant lesions.
95-5459	F	440	BC592	1000 mg/kg	No significant lesions.
95-5460	F	442	BC807	1000 mg/kg	No significant lesions.
95-5461	F	443	BC884	1000 mg/kg	No significant lesions.
95-5462	F	445	BC751	1000 mg/kg	No significant lesions.
95-5463	F	449	BC843	1000 mg/kg	No significant lesions.
95-5464	F	450	BC718	1000 mg/kg	Irregular capsular contours of both pieces.
95-5465	F	451	BC754	1000 mg/kg	No significant lesions.
95-5466	F	453	BC677	1000 mg/kg	No significant lesions.
95-5467	F	459	BC762	1000 mg/kg	No significant lesions.
95-5468	F	465	BC837	1000 mg/kg	No significant lesions.
95-5469	F	466	BC893	1000 mg/kg	No significant lesions.
95-5470	F	471	BC851	1000 mg/kg	No significant lesions.
95-5471	F	472	BC778	1000 mg/kg	No significant lesions.
95-5472	F	475	BC630	1000 mg/kg	No significant lesions.
95-5473	F	477	BC841	1000 mg/kg	One nodule in one, two in other lobes.
95-5474	M	185	BC844	2000 mg/kg	No significant lesions.
95-5475	M	188	BC698	2000 mg/kg	No significant lesions.
95-5476	M	190	BC640	2000 mg/kg	No significant lesions.
95-5477	M	195	BC629	2000 mg/kg	No significant lesions.
95-5478	M	197	BC587	2000 mg/kg	Irregular capsular contusion both lobes.
95-5479	M	199	BC726	2000 mg/kg	No significant lesions.
95-5480	M	200	BC705	2000 mg/kg	Irregular capsular contusion both lobes.
95-5481	M	201	BC731	2000 mg/kg	No significant lesions.
95-5482	M	203	BC846	2000 mg/kg	Nodule in one lobe.
95-5483	M	211	BC763	2000 mg/kg	No significant lesions.
95-5484	M	212	BC700	2000 mg/kg	No significant lesions.
95-5485	M	213	BC805	2000 mg/kg	No significant lesions.
95-5486	M	215	BC670	2000 mg/kg	No significant lesions.
95-5487	M	220	BC661	2000 mg/kg	No significant lesions.
95-5488	M	224	BC775	2000 mg/kg	No significant lesions.
95-5489	M	230	BC788	2000 mg/kg	No significant lesions.
95-5490	M	232	BC749	2000 mg/kg	No significant lesions.
95-5491	M	234	BC639	2000 mg/kg	Irregular capsular contour in one lobe.
95-5492	M	235	BC716	2000 mg/kg	No significant lesions.

R95-5449-5488

Histopathologic Observations:

95-5449
Liver: A few minute foci of mononuclear cell infiltration. Nodular hyperplasia/adenoma of hepatocytes (WS). Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5450
Liver: A few minute foci of mononuclear cell infiltration. Nodular hyperplasia/adenoma of hepatocytes (WS). Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5451
Liver: A few tiny foci of mononuclear cell infiltration. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5452
Liver: A clear cell focus in one lobe. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified infrequently.

95-5453
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5454
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5455
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified infrequently.

95-5456
Liver: Focal peliosis hepatis characterized by sinusoidal dilation filled with blood and hepatocyte hypertrophy in one lobe. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5457
Liver: Leukemia/lymphoma characterized by marked infiltration of lymphoid cells in both lobes. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5458
Liver: Focal hyperplasia in one lobe. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5459
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5460
Liver: Nodular hyperplasia/adenoma of hepatocytes (WS). Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5461
Liver: Minimal mononuclear cell infiltration in a few portal triads in one lobe. Nodular hyperplasia/adenoma of hepatocytes (WS). Warthin-Starry positive bodies compatible with *H. hepaticus* were identified infrequently.

95-5462
Liver: Minimal mononuclear cell infiltration in a few portal areas. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified infrequently.

95-5463
Liver: Nodular hyperplasia/adenoma of hepatocytes (WS). Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.

95-5464
Liver: Nodular hyperplasia/adenoma of hepatocytes (WS). Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.

95-5465
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.

95-5466
Liver: Minimal to mild multifocal mononuclear cell infiltration in the parenchyma and portal triads (leukemia?). Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.

95-5467
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified infrequently.

95-5468
Liver: A few minute foci of hepatocyte degeneration and necrosis with mononuclear cell and neutrophil infiltration in the parenchyma. Nodular hyperplasia/adenoma of hepatocytes in one lobe (WS). Warthin-Starry positive bodies compatible with *H. hepaticus* were identified infrequently.

R95-5449-5492

95-5469
Liver: Two lymphocytic foci around the intralobular bile duct and vein. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5470
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5471
Liver: Nodular hyperplasia/adenoma of hepatocytes in one lobe. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5472
Liver: Minimal mononuclear cell infiltration in a few portal areas. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5473
Liver: Leukemia/lymphoma characterized by marked infiltration of lymphoid cells in both lobes. Nodular hyperplasia/adenoma of hepatocytes with vacuolation (clear cell) in one lobe (WS). Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.
95-5474
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5475
Liver: Nodular hyperplasia/adenoma of hepatocytes in one lobe. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5476
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5477
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified in moderate numbers.
95-5478
Liver: Nodular hyperplasia/adenoma of hepatocytes. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified in moderate numbers.
95-5479
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5480
Liver: Nodular hyperplasia/adenoma of hepatocytes. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5481
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified in moderate numbers.
95-5482
Liver: Nodular hyperplasia/adenoma of hepatocytes. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.
95-5483
Liver: Nodular hyperplasia/adenoma of hepatocytes. Warthin-Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5484
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.
95-5485
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.
95-5486
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5487
Liver: No significant lesions. Warthin Starry positive bodies compatible with *H. hepaticus* were not identified.
95-5488
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.
95-5489
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.
95-5490
Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.

R95-5449-5492

95-5491

Liver: No significant lesions. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified infrequently.

95-5492

Liver: Nodular hyperplasia/adenoma of hepatocytes. Warthin-Starry positive bodies compatible with *H. hepaticus* were identified frequently.

(3/25/96) db
Lab Requests:
( )Micro ( )Hema ( )Sero ( )Para ( )Urin ( )Clin Chem ( )Photos ( ) Specimen Frozen
TISSUE PRESERVATION: ( )Formalin ( )Other Fixative (specify) ( )Freeze -70°C (specify tissues)

AN ASSESSMENT OF NTP'S CONCLUSION THAT TRIETHANOLAMINE CAUSES AN EQUIVOCAL INCREASE IN KIDNEY TUMORS IN MALE FISCHER RATS

Judith A. MacGregor, Ph.D., DABT

January 5, 1996

AN ASSESSMENT OF NTP'S CONCLUSION THAT TRIETHANOLAMINE CAUSES AN EQUIVOCAL INCREASE IN KIDNEY TUMORS IN MALE FISCHER RATS

BACKGROUND: The draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine concludes that treatment with triethanolamine caused an equivocal increase in adenomas in the kidneys of male Fischer rats. The original evaluation of single sections from each kidney showed a borderline increase ($p=0.056$) in adenomas in the mid-dose group, (63 mg/kg), but not in any other treatment group including the high-dose group, (125 mg/kg). A trend test did not show a treatment-related increase in kidney tumors. Because of the marginal nature of the findings, 8 additional step-sections from each male rat were evaluated, 4 from each kidney. Step-sections did not show an increase in either kidney adenomas or hyperplasias in triethanolamine-treated groups. The purpose of this work was to further evaluate the findings to determine if they were in fact consistent with a treatment-related effect, and to determine if NTP's evaluation was consistent with NTP's evaluation of other substances where multiple-section techniques were utilized.

APPROACH: The work was divided into three parts. A) Dr. James Swenberg conducted a microscopic reevaluation of proliferative lesions in kidneys of male rats included in the NTP study. The objective was to determine if classification of the lesions was straightforward and could be made easily and consistently. B) In order to determine if there was statistical support for a treatment-related effect, additional statistical analyses of the histopathologic data in the draft NTP report, as well as an assessment of the diagnoses from the reevaluation by Dr. Swenberg, were conducted. C) Finally, NTP's assessment of triethanolamine was compared to NTP's assessment of other substances for which extra step-sections from male rat kidneys were used to arrive at a final conclusion about their oncogenic potential.

SUMMARY OF KEY FINDINGS AND CONCLUSIONS

1) The proliferative lesion in the male rat kidney is part of a continuum that ranges from mild hyperplasia to at the most extreme, very small adenomas.

2) In many instances it is very difficult to distinguish between severe hyperplasia and adenoma. There are three such cases in the mid-dose group (63 mg/kg triethanolamine), the highest number in any group.

3) The difficulty in making a definitive diagnosis is not mentioned in the draft report, however it is clearly evident from the pathology records. The initial study pathologist only diagnosed 1 of the 7 adenomas that were ultimately reported in the original kidney sections. In other instances, it is so difficult to distinguish between severe hyperplasia and a small adenoma, that subsequent evaluations changed the original diagnosis. For example, a step-section from animal 073 in the low-dose group, diagnosed as having an adenoma by the initial pathologist, was confirmed as an adenoma by the NIEHS pathologist but the Pathology Working Group changed the diagnosis to hyperplasia; only the latter diagnosis was included in the draft final report. Dr. Swenberg diagnosed this lesion as an adenoma, in agreement with the initial diagnoses.

4) Step-sections consisting of eight additional sections from each animal did not confirm the slightly higher number of adenomas in the mid-dose group that were originally found. This is the group suspected by NTP as having the oncogenic response.

5) Only two small adenomas were found in the 392 kidney step-section evaluations of the mid-dose triethanolamine male rats. Dr. Swenberg diagnosed both of these lesions in the mid-dose group to be hyperplasias not adenomas.

6) There were fewer hyperplasias in step-sections from treated animals compared to controls.

7) Because of the difficulty in making a definitive diagnosis, and because the lesions are a part of a continuum, proliferative lesions (hyperplasias and adenomas) should be combined when evaluated for treatment-related effect. When proliferative lesions are combined and considered together, no treatment-related effect is even suggested.

8) There is no statistically significant treatment-related trend for adenoma, hyperplasia or combined proliferative lesions in either step or single sections.

9) Step-section kidney tumor results are statistically different from the single section results. More importantly, the incidence of kidney adenomas in the mid-dose group (63mg/kg) from single sections is statistically different from the incidence of tumors in step-sections.

10) The combined step and single section data in the triethanolamine treated groups fall within the range of the historical control data from 13 studies where step sections were evaluated from male rat kidneys.

11) Other substances that NTP concluded to be equivocal for increasing kidney tumors in male rats all showed a small increase in kidney tumors in step-sections from treated groups compared to controls. Triethanolamine did not.

12) The data on triethanolamine are quite similar to that of toluene, a compound that NTP concluded did not cause an increase in tumors in male rat kidneys because the slight increase in kidney tumors observed in the original sections were not found in the step-sections.

TABLE OF CONTENTS

RESULTS

A) EVALUATION OF PROLIFERATIVE LESIONS IN KIDNEYS OF MALE RATS IN THE CHRONIC STUDY OF TRIETHANOLAMINE

Dr. James Swenberg visited the NTP archives and was able to look at 28 of the male rat kidney sections in which proliferative lesions were diagnosed in both the original sections and additional step-sections. A copy of his report is included under Attachment 1. Although there was reasonably good agreement between his diagnoses and the final diagnoses in the study draft report, there are several new important findings and conclusions. Most significant is the fact that the lesions are extremely small, represent a continuum between hyperplasia and small adenoma and are extremely difficult to differentiate in many cases. Because of these difficulties, Dr. Swenberg recommended that the proliferative lesions should be combined in order to evaluate treatment-related effects. When combined, the incidence of proliferative lesions is 10/50 for controls, 9/50 for the low dose, 11/49 for the mid dose and 8/50 for the high dose groups.

The Pathology Working Group Evaluation of the Selected Proliferative Lesions in the NTP 2-Year Rat Bioassay on Triethanolamine is included in Attachment 2. It clearly shows the difficultly in distinguishing hyperplasia from adenoma because of the number of changes in classification between these two lesions.

Tables of the Diagnoses of Proliferative Lesions in the NTP 2-Year Rat Bioassay on Triethanolamine are included in Attachment 3. Summarized are the results reported in the Draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine for hyperplasia, adenomas and total proliferative lesions. Evident is the lack of any treatment-related effect when proliferative lesions are evaluated together. Also shown, are Dr. Swenberg's evaluations, which differ most significantly from NTP's in that Dr. Swenberg found no additional adenomas in any of the step-sections in the mid-dose animals. Included also are summaries of the individual diagnoses of the proliferative lesions for each group of male rats in the triethanolamine study.

B) FURTHER STATISTICAL ANALYSES OF THE INCIDENCE OF HYPERPLASTIC AND NEOPLASTIC LESIONS IN THE KIDNEY OF MALE RATS FROM THE NTP TRIETHANOLAMINE (TEA) DERMAL STUDY

Further statistical analyses of the hyperplastic and neoplastic lesion data from the kidneys of male rats in the NTP triethanolamine study were conducted by L.G. McFadden; her report is included in Attachment 4. A statistically significant difference in the incidence of adenomas in the original sections compared to the incidence of adenomas in the step-sections was observed. In other words, the original single section and step-section data are statistically different and the incidence of adenomas originally observed is not the same as that observed in the step-sections. The incidence of adenomas in the mid-dose group (63 mg/kg/day) showed a similar statistical difference between the original single sections and the additional step-sections. The purpose of conducting step-sectioning is to help determine whether a marginal increase is really treatment-related, rather than a random occurrence by assessing many more specimens. Step-sections failed to show an increase in adenomas in triethanolamine treated groups. In fact, the incidence of hyperplasias in the control animals is higher than that in the treated groups in step-section specimens.

Dr. Swenberg concluded that two of the lesions in the mid-dose group that were classified as adenomas in the draft NTP report were hyperplasias. Swenberg's data for adenomas from single and step sections in the mid dose group, the group that NTP believed to be affected by treatment, did not approach significance ($p=0.175$).

All trend tests for adenomas, hyperplasias, and combined proliferative lesions in the original and step-section data were not significant. This was true for the NTP and Swenberg data sets and further supports the lack of any treatment-related effect.

C) REVIEW OF NTP STUDIES IN WHICH STEP-SECTIONS OF KIDNEYS FROM MALE FISCHER RATS WERE EVALUATED TO DETERMINE THEIR ONCOGENIC POTENTIAL.

In a recent review of 379 carcinogenicity studies in rodents conducted by the National Cancer Institute and the National Toxicology Program, the kidneys were the third most frequent site for chemical-related neoplasia (Huff, 1991). While many compounds

produced large increases in the incidences of renal neoplasms, some compounds

produced marginal increases that made definitive conclusions about their oncogenic activity difficult. To help NTP in their interpretation, multiple step-sections were evaluated histopathologically.

Eustis et al. (1994) summarized 13 chronic NTP studies in which multiple step-sections of male rat kidneys were evaluated in order to determine if the treatment was the cause of the very slight increase in the incidence of proliferative lesions observed in the original pathological assessment of one section from each kidney. Multiple-sections involved obtaining an additional 6-8 sections at 1 mm intervals from each rat kidney. While the incidence of kidney tumors in the original sections in control male rat kidneys from the 13 studies ranged from 0 to 2%, when multiple sections were evaluated the incidence of kidney tumors ranged from 0 to 16%. The mean incidence of proliferative lesions was markedly higher in multiple section evaluation of control kidneys: hyperplasias increased 177%, adenomas increased 621% and the incidence of total kidney tumors (adenomas + carcinomas) increased 500%. This pattern of a dramatic increase in the incidence of kidney proliferative lesions, however, was not found in the triethanolamine study. In the mid-dose group, the group with the highest incidence of tumors and the one NTP was concerned showed a possible treatment-related increase in tumors, the incidence of hyperplasias was 8% in the single sections and 12% after multiple sections. Dr. Swenberg's evaluation was identical for single or multiple sections (8%). These results appear consistent with the conclusion that the higher incidence of tumors in the triethanolamine study were a chance occurrence in the original evaluation, since multiple sections failed to confirm the occurrence of additional tumors.

In the 13 studies in which NTP analyzed multiple sections, 9 substances were clearly shown to give a significant number of additional kidney tumors and were concluded to have some evidence of oncogenicity. Three compounds, phenylbutazone, furosemide, and CI Pigment Red 23, were classified as equivocal after the extended evaluation. All three had at least a slight increase in kidney tumors that was apparent in both the original and extended evaluation (see Table 1). In addition, this increase was statistically significant in the low-dose phenylbutazone group. Both furosemide and CI Pigment Red 23 had an increase in the incidence of hyperplastic lesions in the high dosage group. In contrast, the extended evaluations of triethanolamine showed a similar incidence of adenomas across all groups and more hyperplastic lesions in the

controls than in the high dosage group. These results are similar to those for toluene, the only compound NTP concluded to be negative after evaluation of extended sections of kidney from male rats. The incidence of hyperplasia and adenomas in the kidneys of toluene-treated male rats was similar to the controls. It is not clear what criteria are being used by NTP to classify studies when additional step-sections are obtained in order to resolve difficulties in interpretation. Step sectioning is conducted to provide the additional data and should be utilized consistently.

TABLE 1

COMPARISON OF NTP MULTIPLE-SECTION SAMPLING OF MALE RAT KIDNEY WITH ORIGINAL SINGLE-SECTION EVALUATIONS

COMPOUND	ORIGINAL EVALUATION		MULTIPLE-SECTION EVALUATION		NTP CLASSIFICATION
LESION	HYPERPLASIA	TUMORS	HYPERPLASIA	TUMORS	
TEA	No Effect	Slight Increase-Mid Dose	Controls Higher	Similar to Control	EQUIVOCAL
TOLUENE	No Effect	Slight Increase-Both Doses	No Effect	Similar to Control	NEGATIVE
PHENYLBUTAZONE	Similar to Controls	Slight Increase-High Dose	Similar to Controls	Significant Increase	EQUIVOCAL
FUROSEMIDE	No Effect	Slight Increase-Low Dose	Slight Increase-High Dose	Slight-Increase High Dose	EQUIVOCAL
CI PIGMENT RED 23	Increase-High Dose	Slight Increase-High Dose	Increase-High Dose	Slight-Increase High Dose	EQUIVOCAL

REFERENCES

Draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine (Cas no. 102-71-6) in F344/N Rats and B6C3F1 Mice (Dermal Studies). NTP TR 449, NIH Pub. No. 94-3365, U. S. Public Heath Service, NIH.

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PATHOLOGICAL REVIEW OF SLIDES
FROM THE NTP 2-YEAR RAT BIOASSAY
ON TRIETHANOLAMINE

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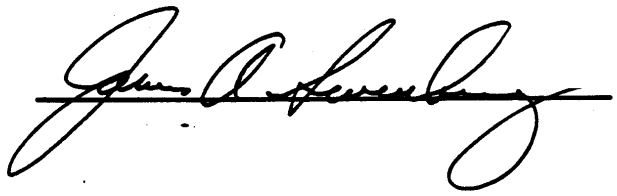
August 30, 1995



Introduction

I was asked to visit the National Toxicology Program Archives in Research Triangle Park, NC to review the kidney slides of the 2-year rat carcinogenicity bioassay on triethanolamine (NTP Technical Report No. 449) that were identified as having either renal adenoma or hyperplasia, and to evaluate the kidney slides from male rats in the associated 13-week study for the presence of lesions compatible with alpha$_{2u}$-globulin nephropathy. The visit took place on June 21, 1995, and the results are reported below.

Results

Table 1 provides data on the diagnoses of the original sections from the 2-year rat study on triethanolamine for the study pathologist, QA pathologist, PWG pathologist, PWG consensus, as well as mine. The most striking feature of this table is the fact that the original pathologist only diagnosed one renal adenoma out of the 7 that were ultimately identified by the PWG. The QA pathologist identified two additonal adenomas, although since the kidney had not been identified as a tatget tissue, not all kidney sections were examined. After this, the kidney was identified as a possible target tissue and the PWG Chairperson was asked to re-examine all male and female kidneys for proliferative lesions. It should not be surprising therefore, that the the PWG identified more kidney tumors than the QA pathologist. The fact that the original pathologist only identified one of the 7 adenomas atests to the small size of the lesions. In fact, there is no clear distinction between the larger hyperplasias and the smaller adenomas. Thus, it is reasonable to consider these two diagnoses as a continuum and to add the total number of such lesions when evaluating the evidence for a dose-response relationship between exposure and the induction of renal preneoplastic and neoplastic lesions. Case 88, a low dose male, had a very early lesion that was called hyperplasia by the PWG Chairperson and nephropathy by the PWG. I agreed with the PWG Chairperson. Rat 130, a middle dose male, had very similar lesion. Diagnoses on the original slides were the only material that was suitable for comparison to historical controls, due to the number of sections being evaluated.

Table 2 shows the diagnoses on the additional step sections of male rat kidneys. This table includes the diagnoses of the initial reviewer from Pathco, the NTP internal reviewer, the second PWG consensus, and my diagnoses. There was good agreement between the various reviewers. However, it is also clear that the lesions represent a continuum from hyperplasia to microscopic adenoma. I have put an asterick by the 8 cases that could either be diagnosed as severe hyperplasia or adenoma. This clearly suggests that the best interpretation of the study is achieved by combining hyperplasia and adenoma. When this is done for the 24 month study, the incidence of renal proliferative lesions is 10/50 for controls, 9/50 for low dose, 11/49 for the middle dose, and 8/50 for the high dose male rats. Thus it is clear that there is no exposure-response relationship between triethanolamine and the induction of proliferative renal lesions.

Table 3 contains the results of my review of the control and high dose male rat kidney sections from the 13-week study. It is clear that no renal pathology was present. This is in agreement with NTP Technical Report 449. Thus, there is no evidence for the induction of $alpha_{2U}$-globulin nephropathy by triethanolamine.

Discussion

My review of the kidney sections from the NTP studies on triethanolamine is in close agreement with NTP Technical Report 449. There were no serious disagreements with the diagnoses used in the report and there was no clear distinction between the larger hyperplasias and the smaller adenomas. Thus, it is reasonable to consider these two diagnoses as a continuum and to add the total number of such lesions when evaluating the evidence for a dose-response relationship between exposure and the induction of renal preneoplastic and neoplastic lesions. When renal hyperplasia and adenoma were combined for the 24 month study, there were 10/50, 9/50, 11/49 and 8/50 in the control, low, middle and high dose males. It is clear that no exposure-response relationship exists for renal proliferative lesions and triethanolamine.

Table 1. Diagnoses on the original male rat kidney slides from the 2-year triethanolamine bioassay.

Animal	Group	Study Path.	QA Path.	PWG Chair	PWG Final	J. Swenberg
020	CM	-	NR	Hyp2	Hyp2	Hyperplasia-moderate
062	LM	-	NR	Ad	Ad	Adenoma, small
088	LM	-	NR	Hyp1	Neph	Hyperplasia, mild
123	MM	Ad	Ad	Ad	Ad	Adenoma
130	MM	-	NR	Hyp1	Hyp1	Hyperplasia, slight
149	MM	-	Ad	Ad	Ad	Adenoma
151	MM	-	NR	Ad	Ad	Adenoma
163	MM	-	NR	Ad	Ad	Adenoma
196	HM	-	NR	Ad	Ad	Adenoma
212	HM	-	Ad	Ad Hyp2	Ad Hyp2	Adenoma and hyperplasia, moderate

Note: Ad is adenoma, NR is Not Reported, Hyp1 is slight to mild hyperplasia, while Hyp2 is moderate hyperplasia. CM, LM, MM, and HM refer to control, low, middle, and high dose males.

Table 2. Diagnoses on the step-section male rat kidney slides from the 2-year triethanolamine bioassay.

Animal	Group	Initial Path.	NIEHS Path.	PWG	J. Swenberg
021	CM	Ad	Ad	Hyp	Hyperplasia, severe*
026	CM	Ad	Ad	Ad	Adenoma
062	LM	Hyp	Hyp	Hyp	Hyperplasia, severe*
073	LM	Ad	Ad	Hyp	Adenoma, small*
081	LM	Hyp	Hyp	Hyp	Hyperplasia, severe*
088	LM	Onc	Onc	Onc	Oncocytoma, small
110	LM	Ad	Ad	Hyp	Hyperplasia, severe*
113	LM	Ad Ad	Ad Ad	Hyp Ad	Hyperplasia, moderate Adenoma
120	LM	Ad	Hyp	Hyp	Hyperplasia, moderate Hyperplasia, slight
130	MM	-	Hyp	-	Hyperplasia, slight
156	MM	Ad & Hyp	Ad & Hyp	Ad & Hyp	Hyperplasia, severe* & hyperplasia, moderate
167	MM	-	Ad	Ad & Hyp	Hyperplasia, severe*& hyperplasia, slight & renal sarcoma, large
170	MM	Hyp	Hyp	Hyp	Hyperplasia, cystic
173	MM	Hyp	Hyp	Hyp	Hyperplasia, severe*
182	HM	Ad	Ad	Hyp	Hyperplasia, moderate
197	HM	Ad & Hyp	Ad & Hyp	Ad & Hyp	Adenoma & hyperplasia, moderate (1-2) Hyperplasia, slight (2-1)
216#	HM	Ad	Ad	Ad	Adenoma
239	HM	Ad	Ad	Ad	Adenoma, small

Ad, adenoma; Hyp, hyperplasia (no grade given); *, Diagnosis could either be adenoma or hyperplasia; for animal 197, the numbers in parentheses is the slide number. #, Rat 216 was an interim sacrifice animal and is not included in the tabulated results of the 24 month study.

Table 3. Histopathologic examination for protein droplets in control and high dose male rats in the 13 week NTP study on triethanolamine.

Animal	Group	Diagnosis
11	CM	NVL
12	CM	NVL
13	CM	NVL
14	CM	NVL
15	CM	NVL
16	CM	NVL
17	CM	NVL
18	CM	NVL
19	CM	NVL
20	CM	NVL
111	HM	NVL
112	HM	NVL
113	HM	NVL
114	HM	NVL
115	HM	NVL
116	HM	NVL
117	HM	NVL
118	HM	NVL
119	HM	NVL
120	HM	NVL

CM is the control male group; HM is the high dose male group (2.0 g/kg); NVL, no visible lesion

CHAIRPERSON'S REPORT
SPECIAL NTP PATHOLOGY WORKING GROUP REVIEW
KIDNEY STEP-SECTIONS OF MALE F344 RATS FROM
CHRONIC DERMAL TRIETHANOLAMINE (C61621D) STUDY

Prepared by:
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Conflict of Interest Statement:

NIEHS employee Dr. Ann Radovsky served both as the quality assessment pathologist and the chairperson for this Special NTP Pathology Working Group Review held September 3, 1993. She has not been involved in the testing or evaluation of Triethanolamine (C61621D) in any other capacity at any other time.

Ann Radovsky, DVM
9/23/93

NARRATIVE

Following the Pathology Working Group meetings of Dec.10, 1992 (where predetermined "target organs" were reviewed,) and of February 9, 1993 (where the "reviewed" initial kidney slides were studied), all kidneys of male rats in the study were retrieved from the vet tissues and step-sectioned at approximately 0.5 mm intervals so that four sections of each kidney were obtained. These step-sections from all 239 male rats in the chronic study were examined for renal proliferative lesions by Dr. Hildebrandt, PATHCO (Draft received May 20, 1993).

In July, 1993, Dr. Radovsky at NIEHS further examined ("Quality Assessment") the kidney step-sections kidneys as follows:

1.) All sections from rats identified as having proliferative kidney lesions (hyperplastic and/or neoplastic) by Dr. Hildebrandt were reviewed;

2.) All sections from the rats identified by the PWG as having proliferative kidney lesions were reviewed; and

3.) All sections from an arbitrary 10% of the remaining rats in each treatment group were reviewed.

The total number of animals in "QA" assessment was 64 of 239 male rats.
(19/60 control; 17/60 low dose; 26/59 mid-dose; and 12/60 high dose)

In the QA review, and in instructions to the Special PWG, the following criteria for proliferative lesions of renal tubular epithelium were used:

Kidney, renal tubule-hyperplasia:

-polygonal tubular epithelial cells with no more than mild atypia, either filling, or in multiple strata, in tubules at least 2 or 3 times the diameter of normal tubules. Tubule basement membranes no more than the thickness of one epithelial cell layer. Masses of tubular epithelium containing a central cavity and inflammatory cells could represent reaction to tubular inflammation or central necrosis in a proliferative mass. Cystic, as a modifier of hyperplasia, was **not** used because it was not considered to contribute any meaningful information. Enlarged tubules layered with brightly eosinophilic epithelial cells containing numerous fine granules (oncocytic hyperplasia), were not separately categorized.

Kidney, renal tubule - adenoma:

- well-circumscribed discrete mass of epithelial cells with no

more than mild atypia and neither basement membrane dependence or definite tubular structure; at least 5X the diameter of normal tubules.

Kidney - oncocytoma, benign:
- well-circumscribed discrete mass of brightly eosinophilic epithelial cells containing numerous fine granules, lacking either dependence on a basement membrane or definite tubular structure.

Kidney, renal tubule - carcinoma:
- large-sized (1 cm. dia.) mass of epithelial cells with increased cellular anaplasia, unorganized growth pattern and increased vascularity.

A total of 20 microscopic slides from 18 animals were presented to the Special NTP PWG. These slides included all differences of opinion between the PATHCO diagnoses and those of the QA pathologist and included all lesions evaluated by either the PATHCO or the QA pathologist as neoplastic.

At the Special NTP PWG:
- there was general agreement that the use of the modifier "cystic" for hyperplastic lesions of enlarged tubules was unnecessary;
- four renal tubule proliferative lesions previously evaluated as benign neoplasms were evaluated as hyperplastic lesions;
- there was general agreement that the continuum of renal tubule proliferative lesions from hyperplasia to benign neoplasia to malignant neoplasia was gradual and complicated the categorization of many of the lesions evaluated;
- lesions (evaluated as adenomas), present in two step sections on the same microscopic slide (slide 1-2 from high dose male 00197) were considered to represent a single neoplastic proliferation. It was noted that rat kidney step-sections are instructed to be cut at an interval of 1.0 mm between sections, and that the 0.5 mm interval used in the present study was an error;
- finally, it was noted that the hemangiosarcoma present in sections from one mid-dose male (00167) was not noted in any other organ and may have been primary in the kidney.

Attached are the following:
1) Dr. Hildebrandt's (PATHCO) draft reporting his diagnoses of all step-sectioned kidneys.
2) A comparison table of Dr. Hildebrandt's (PATHCO) diagnoses with those kidneys in the QA review, including notes of the results of the PWG of the initial kidney sections (2/9/93), and of the present Special NTP PWG of the kidney step-sections (9/3/93).
3) The signature page from the present Special NTP PWG.
4) The diagnoses from the present Special NTP PWG.
5) A summary table of the renal tubule proliferative lesions observed in the step sections as determined by the present Special NTP PWG.

Triethanolamine (C61621B) Rat Kidney Step Sections
Control (0 mg/kg) males

Animal	Slide	PATHCO Diagnosis	Reviewer Diagnosis
(NPL = No Proliferative Lesions of renal tubules)			
00001	All	NPL	NPL
Comment: Sections had autolysis.			
00003	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	Hyperplasia, min.	Hyperplasia, min.;
	2-2	NPL	NPL
00004	1-1	NPL	NPL
	1-2	Hyperplasia, mild	Hyperplasia, mild
	2-1	NPL	NPL
	2-2	Hyperplasia, mild	Hyperplasia, mild
00006	1-1	Hyperplasia, min.	Hyperplasia, min
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Cystic tubule	NPL
00007	1-1	Hyperplasia, min.	Hyperplasia, min
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	NPL	NPL
00015	1-1	NPL	Hyperplasia, min
	1-2	Hyperplasia, min.	Hyperplasia, min.
	2-1	NPL	NPL
	2-2	NPL	NPL
Slides Rats			
00016	All	NPL	NPL
Comment: Sections had autolysis.			
00020	All	NPL	NPL
Comment: PWG (2/9/93) slide had moderate hyperplasia, not noted in these step sections.			
00021	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Tubular adenoma	Renal tubule, adenoma
SPECIAL NTP PWG (9/3/93) EVALUATED LESION ON SLIDE 2-2 AS RENAL TUBULE, HYPERPLASIA.			

00025	All	NPL	NPL
00026	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Tubular adenoma	Renal tubule, adenoma

SPECIAL NTP PWG (9/3/93) CONFIRMED LESION ON SLIDE 2-2 AS RENAL TUBULE, ADENOMA.

00028	All	NPL	NPL
00032	1-1	NPL	Mesothelioma
	1-2	NPL	Mesothelioma
	2-1	NPL	Mesothelioma
	2-2	Mesothelioma	Mesothelioma
00036	All	NPL	NPL
00044	All	NPL	NPL
00051	All	NPL	NPL
00052	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	Hyperplasia, min.	Hyperplasia, min., multiple
	2-2	NPL	NPL
00058	All	NPL	NPL
00060	1-1	Hyperplasia, min.	Hyperplasia, min
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	NPL	NPL

Triethanolamine (C61621B) Rat Kidney Step Sections
Low dose (32 mg/kg) males

Animal	Slide	PATHCO Diagnosis	Reviewer Diagnosis
00061	All	NPL	NPL
00062	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	Cystic hyperplasia, moderate	Renal tubule,hyperplasia, moderate
	2-2	NPL	NPL

Comment: PWG (2/9/93) slide had an adenoma, not noted in these step sections. SPECIAL NTP PWG (9/3/93) EVALUATED LESION ON SLIDE 2-1 AS RENAL TUBULE, HYPERPLASIA.

00066	All	NPL	NPL
00068	1-1	Hyperplasia, min.	Hyperplasia, min.
	1-2	Hyperplasia, min.	Hyperplasia, min.
	2-1	NPL	NPL
	2-2	NPL	NPL
00073	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Tubular adenoma	Renal tubule, adenoma

SPECIAL NTP PWG (9/3/93) EVALUATED LESION ON SLIDE 2-2 AS RENAL TUBULE, HYPERPLASIA.

00078	All	NPL	NPL
00081	1-1	Cystic hyperplasia, min.	Hyperplasia min.
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	NPL	NPL

SPECIAL NTP PWG (9/3/93) CONFIRMED LESION ON SLIDE 1-1 AS RENAL TUBULE, HYPERPLASIA.

00086	All	NPL	NPL
00088	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	Oncocytoma	Oncocytoma
	2-2	NPL	NPL

Comment: PWG (2/9/93) slide had diagnosis of minimal nephropathy. SPECIAL NTP PWG (9/3/93) CONFIRMED LESION ON SLIDE 2-1 AS ONCOCYTOMA.

00092	All	NPL	NPL
00098	All	NPL	NPL
00104	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Hyperplasia, min.	Hyperplasia, min.
00110	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	Tubular adenoma	Renal tubule, adenoma
	2-2	NPL	NPL

SPECIAL NTP PWG (9/3/93) EVALUATED LESION ON SLIDE 2-1 AS RENAL TUBULE, HYPERPLASIA.

00111	All	NPL	NPL
00113	1-1	Tubular adenoma	Renal tubule, hyperplasia
	1-2	NPL	NPL
	2-1	Tubular adenoma	Renal tubule, adenoma
	2-2	NPL	NPL

SPECIAL NTP PWG (9/3/93) EVALUATED LESION ON SLIDE 1-1 AS RENAL TUBULE, HYPERPLASIA, AND CONFIRMED LESION ON SLIDE 2-1 AS RENAL TUBULE, ADENOMA. Note that there are both hyperplastic and neoplastic proliferative lesions in this animal's kidneys.

00117	All	NPL	NPL
00120	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Tubular adenoma	Renal tubule, hyperplasia, mod.

SPECIAL NTP PWG (9/3/93) EVALUATED LESION ON SLIDE 2-2 AS RENAL TUBULE, HYPERPLASIA.

Triethanolamine (C61621B) Rat Kidney Step Sections
Middle dose (63 mg/kg) males

Animal	Slide	PATHCO Diagnosis	Reviewer Diagnosis
00121	All	NPL	NPL
00123	All	NPL	NPL

Comment: PWG (2/9/93) slide had an adenoma, not noted in these step sections.

00128	All	NPL	NPL
00130	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	NPL	Renal tubule, hyperplasia, mod.

Comment: PWG (2/9/93) slide had minimal hyperplasia. SPECIAL NTP PWG (9/3/93) EVALUATED SLIDE 2-2 AS HAVING NO RENAL TUBULE PROLIFERATIVE LESIONS.

00136	All	NPL	NPL
00145	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	Hyperplasia, min	Hyperplasia, min.
	2-2	NPL	NPL
00146	All	NPL	NPL

Comment: Section has autolysis.

00149	1-1	NPL	Mesothelioma
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	NPL	NPL

Comment: PWG (2/9/93) slide had a renal tubule adenoma, not noted in these step sections.

00151	All	NPL	NPL

Comment: PWG (2/9/93) slide had a renal tubule adenoma, not noted in these step sections.

00154	1-1	NPL	NPL
	1-2	Hyperplasia, mild	Hyperplasia, mild
	2-1	NPL	NPL
	2-2	NPL	NPL

00156	1-1	NPL	NPL
	1-2	Tubular adenoma; Hyperplasia, mod.	Renal tubule, adenoma; Renal tubule, hyperplasia, mod.
	2-1	NPL	NPL
	2-2	NPL	NPL

SPECIAL NTP PWG (9/3/93) CONFIRMED SLIDE 1-2 AS HAVING TWO RENAL TUBULE PROLIFERATIVE LESIONS, AN ADENOMA AND FOCAL HYPERPLASIA.
Comment: There are both hyperplastic and neoplastic lesions in this case.

00160	All	NPL	NPL

00163	All	NPL	NPL

Comment: PWG (2/9/93) slide had adenoma, not noted in these serial sections.

00166	All	NPL	NPL

Comment: Sections have autolysis.

00167	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	Adenoma; Hemangiosarcoma
	2-2	NPL	NPL

SPECIAL NTP PWG (9/3/93) EVALUATED SLIDE 2-1 AS HAVING TWO RENAL TUBULE PROLIFERATIVE LESIONS, AN ADENOMA AND FOCAL HYPERPLASIA, AND CONFIRMED PREVIOUSLY DIAGNOSED HEMANGIOSARCOMA. IT WAS NOTED THAT HEMANGIOSARCOMA WAS NOT OBSERVED IN ANY OTHER ORGAN IN THIS ANIMAL.
Comment: There are both hyperplastic and neoplastic lesions in this case.

00170	1-1	NPL	NPL
	1-2	Cystic hyperplasia, min.	Renal tubule, hyperplasia, min.
	2-1	NPL	NPL
	2-2	NPL	NPL

SPECIAL NTP PWG (9/3/93) EVALUATED SLIDE 1-2 AS RENAL TUBULE, HYPERPLASIA.

00172	ALL	NPL	NPL

00173	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Cystic hyperplasia, min.	Renal tubule, hyperplasia, min.

SPECIAL NTP PWG (9/3/93) EVALUATED SLIDE 1-2 AS RENAL TUBULE, HYPERPLASIA.

00176	All	NPL	NPL
00178	1-1	NPL	NPL
	1-2	NPL	NPL
7	2-1	NPL	NPL
	2-2	Hypertrophy, mod.	Hypertrophy, mod.

Triethanolamine (C61621B) Rat Kidney Step Sections
High dose (125 mg/kg) Males

Animal	Slide	PATHCO Diagnosis	Reviewer Diagnosis
00181	All	NPL	NPL
00182	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Tubular adenoma	Renal tubule, adenoma
SPECIAL NTP PWG (9/3/93) EVALUATED LESION ON SLIDE 2-2 AS RENAL TUBULE, HYPERPLASIA.			
00185	1-1	NPL	NPL
	1-2	Hyperplasia, min.	Hyperplasia, min.
	2-1	NPL	NPL
	2-2	NPL	NPL
00189	All	NPL	NPL
00191	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Hyperplasia, marked	Hyperplasia, marked
00196	All	NPL	NPL
Comment: PWG (2/9/93) slide had a renal tubule adenoma, not noted in these step sections.			
00197	1-1	NPL	NPL
	1-2	Tubular adenoma	Renal tubule, adenoma
	2-1	NPL	NPL
	2-2	Hyperplasia, mild	Hyperplasia, mild
SPECIAL NTP PWG (9/3/93) CONFIRMED LESION ON SLIDE 1-2 AS RENAL TUBULE, ADENOMA AND THAT ON SLIDE 2-2 AS RENAL TUBULE, HYPERPLASIA. Comment: Both neoplasia and hyperplasia are in this case.			
00199	All	Mesothelioma	Mesothelioma
00203	All	NPL	NPL
00206	All	NPL	NPL

00212	All	NPL	NPL

Comment: PWG (2/9/93) slide had both renal tubule,adenoma and renal tubule, hyperplasia (neoplasia and hyperplasia), neither noted in these step sections.

00216	1-1	NPL	NPL
	1-2	Tubular adenoma	Renal tubule, adenoma
	2-1	NPL	NPL
	2-2	NPL	NPL

SPECIAL NTP PWG (9/3/93) CONFIRMED LESION ON SLIDE 1-2 AS RENAL TUBULE, ADENOMA.

00217	All	NPL	NPL
00225	All	NPL	NPL
00231	All	NPL	NPL
00233	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Hyperplasia, min.	Hyperplasia, min.
00235	All	NPL	NPL

Comment: Slides have autolysis.

00239	1-1	NPL	NPL
	1-2	NPL	NPL
	2-1	NPL	NPL
	2-2	Tubular adenoma	Renal tubule, adenoma

SPECIAL NTP PWG (9/3/93) CONFIRMED LESION ON SLIDE 2-2 AS RENAL TUBULE, ADENOMA.
Comment: Slides have autolysis.

SPECIAL PWG

NTP PATHOLOGY WORKING GROUP
FOR

Chemical Name Triethanolamine Chemical Number C61621D

Experiment Number 05109 Test #/Species 11/Rats

Date of PWG September, 03, 1993 *Review of Kidney Proliferative Lesions.

****

PARTICIPANTS

Chairperson/Affiliation		Signature
Ann Radovsky, D.V.M., Ph.D.	NIEHS	Ann Radovsky
Members/Affiliation		**Signature**
James Hailey, D.V.M.	NIEHS	
Michael Elwell, D.V.M., Ph.D.	NIEHS	
Darlene Dixon, D.V.M., Ph.D.	NIEHS	
Akiko Enomoto, D.V.M.	NIEHS	
Ronald Herbert, D.V.M., Ph.D.	NIEHS	

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PATHOLOGY WORKING GROUP DIAGNOSES

Chemical Name Triethanolamine (Review of Kidney Step-Sections) Chemical Number C61621D

Species Rat Sex Male Date September 3, 1993

Group/CID Number	No Sis.	Organ/Site	Initial Reviewer's Diagnosis	Internal (NIEHS) Reviewer's Diagnosis	Pathology Working Group Comments or Diagnosis
MM/00156	1	Kidney, (1-2) Renal Tubule	Adenoma; Hyperplasia	Adenoma; Hyperplasia	Adenoma; Hyperplasia
MM/00167	1	Kidney, (2-1) Renal Tubule	No Prolif Lesion (Hemangiosarc)	Adenoma	Adenoma; Hyperplasia
MM/00170	1	Kidney, (1-2) Renal Tubule	Cystic hyperplasia	Hyperplasia	Hyperplasia
MM/00173	1	Kidney, (2-2) Renal tubule	Cystic hyperplasia	Hyperplasia	Hyperplasia
HM/00182	1	Kidney, (2-2) Renal tubule	Adenoma	Adenoma	Hyperplasia
HM/00197	2	Kidney, (1-2) (2-2) Renal tubule	Adenoma; Hyperplasia	Adenoma; Hyperplasia	Adenoma; Hyperplasia
HM/00216	1	Kidney, (1-2) Renal tubule	Adenoma	Adenoma	Adenoma
HM/00239	1	Kidney, (2-2) Renal tubule	Adenoma	Adenoma	Adenoma

Ann Radovsky 9/1/93

PATHOLOGY WORKING GROUP DIAGNOSES

Chemical Name Triethanolamine (Review of Kidney Step-Sections) Chemical Number C61621D

Species Rat Sex Male Date September 3, 1993

Group/CID Number	No Sts.	Organ/Site	Initial Reviewer's Diagnosis	Internal (NIEHS) Reviewer's Diagnosis	Pathology Working Group Comments or Diagnosis
CM/00021	1	Kidney (2-2)	Adenoma	Adenoma	Hyperplasia
CM/00026	1	Kidney (2-2)	Adenoma	Adenoma	Adenoma
LM/00062	1	Kidney (2-1)	Cystic hyperplasia	Hyperplasia	Hyperplasia
LM/00073	1	Kidney (2-2)	Adenoma	Adenoma	Hyperplasia
LM/00081	1	Kidney (1-1)	Hyperplasia	Hyperplasia	Hyperplasia
LM/00088	1	Kidney (2-1)	Oncocytoma	Oncocytoma	Oncocytoma
LM/00110	1	Kidney (2-1)	Adenoma	Adenoma	Hyperplasia
LM/00113	2	Kidney (1-1) (2-1)	Adenoma Adenoma	Adenoma Adenoma	Hyperplasia Adenoma
LM/00120	1	Kidney (2-2)	Adenoma	Hyperplasia	Hyperplasia
MM/00130	1	Kidney (2-2)	No Prolif. Lesion	Hyperplasia	No Prolif. Lesion

Ann Radovsky

SUMMARY OF RENAL TUBULE PROLIFERATIVE LESIONS IN STEP SECTIONS OF MALE F344 RATS EXPOSED TO CHRONIC DERMAL TRIETHANOLAMINE (BASED ON SPECIAL NTP PWG [9/2/93] OR CONCORDANCE BETWEEN PATHCO AND REVIEWING PATHOLOGIST)

	0 MG/KG	32 MG/KG	63 MG/KG	125 MG/KG
ADENOMA	1	1 (1*)	2 (2*)	3 (1*)
ONCOCYTOMA	0	1	0	0
HYPERPLASIA	8	8	6	5

(#*) indicates number of animals with both neoplastic and hyperplastic lesions.

SUMMARY

TRIETHANOLAMINE NTP CHRONIC STUDY
MALE RAT KIDNEY PROLIFERATIVE LESIONS

STUDY RESULTS TRIETHANOLAMINE	CONTROL	LOW	MID	HIGH
HYPERPLASIA NTP Single	1	0	1	1
HYPERPLASIA NTP Total	9	8	7	6
HYPERPLASIA Swenberg Single	1	1	1	1
HYPERPLASIA Swenberg Total	9	8	7	6
TUMORS Adenomas Total NTP	1	2	6	4
TUMORS Adenomas Total Swenberg	1	3	4	4
PROLIFERATIVE LESIONS NTP	10	8	11	8
PROLIFERATIVE LESIONS Swenberg	10	9	11	8

TRIETHANOLAMINE NTP CHRONIC STUDY

MALE RAT KIDNEY PROLIFERATIVE LESIONS

CONTROLS

ANIMAL #	Step or Regular	NTP	SWENBERG
3	S	Hyperplasia	
4	S	Hyperplasia	
6	S	Hyperplasia	
7	S	Hyperplasia	
15	S	Hyperplasia	
16	S	NPL	
20	S	NPL	
20	R	Hyperplasia	Hyperplasia
21	S	Hyperplasia	Hyperplasia
25	S	NPL	
26	S	Adenoma	Adenoma
28	S	NPL	
32	S	Mesothelioma	
36	S	NPL	
44	S	NPL	
51	S	NPL	
52	S	Hyperplasia	
58	S	NPL	
60	S	Hyperplasia	

NPL= No Proliferative Lesion

TRIETHANOLAMINE NTP CHRONIC STUDY

MALE RAT KIDNEY PROLIFERATIVE LESIONS

LOW DOSE

ANIMAL #	Step or Regular	NTP	SWENBERG
61	S	NPL	
62	S	Hyperplasia	Hyperplasia
62	R	Adenoma	Adenoma
66	S	NPL	
68	S	Hyperplasia	
73	S	Hyperplasia	Adenoma
81	S	Hyperplasia	Hyperplasia
88	S	Oncocytoma	Oncocytoma
88	R	Nephropathy	Hyperplasia
104	S	Hyperplasia	
110	S	Hyperplasia	Hyperplasia
113	S	Hyperplasia + Adenoma	Hyperplasia + Adenoma
120	S	Hyperplasia	Hyperplasia

TRIETHANOLAMINE NTP CHRONIC STUDY

MALE RAT KIDNEY PROLIFERATIVE LESIONS

MID DOSE

ANIMAL #	Step or Regular	NTP	SWENBERG
123	R	Adenoma	Adenoma
130	S	NPL	Hyperplasia
130	R	Hyperplasia	Hyperplasia
145	S	Hyperplasia	
149	R	Adenoma	Adenoma
151	R	Adenoma	Adenoma
154	S	Hyperplasia	
156	S	Adenoma + Hyperplasia	Hyperplasia + Hyperplasia
163	R	Adenoma	Adenoma
167	S	Adenoma + Hyperplasia	Hyperplasia + Hyperplasia
170	S	Hyperplasia	Hyperplasia
173	S	Hyperplasia	Hyperplasia

TRIETHANOLAMINE NTP CHRONIC STUDY

MALE RAT KIDNEY PROLIFERATIVE LESIONS

HIGH DOSE

ANIMAL #	Step or Regular	NTP	SWENBERG
182	S	Hyperplasia	Hyperplasia
185	S	Hyperplasia	
191	S	Hyperplasia	
196	R	Adenoma	Adenoma
197	S	Adenoma + Hyperplasia	Adenoma + Hyperplasia
212	R	Adenoma + Hyperplasia	Adenoma + Hyperplasia
216 Interim Sac	S	Adenoma	Adenoma
233	S	Hyperplasia	
239	S	Adenoma	Adenoma

SUMMARY OF FURTHER STATISTICAL ANALYSES OF THE INCIDENCE OF HYPERPLASTIC AND NEOPLASTIC LESIONS IN THE KIDNEY OF MALE RATS FROM THE NTP TRIETHANOLAMINE (TEA) DERMAL STUDY

These analyses were done to further analyze the equivocal findings from the NTP TEA study. The data considered are the number of hyperplasias and adenomas in single sections (1 per kidney) and step sections (4 additional per kidney), plus various combinations of these, for the male rat kidneys at 2 years. Also addressed are the data from the re-evaluation of the male rat kidney lesions by Dr. James A. Swenberg (University of North Carolina). The combined single and step sections will be referred to as "total sections". Combined hyperplasias and adenomas will be referred to as "proliferative lesions". The Cochran-Armitage trend test (Armitage, 1971) and the Fisher exact probability test (Siegel, 1956) were used to analyze the data. The trend test was conducted at the significance level of alpha=0.02, two-sided. Fisher's exact test was used to compare the incidence of lesions in each of the treated groups to the control group of rats and was conducted at the significance level of alpha=0.05, one-sided.

The NTP based its determination of equivocal evidence of carcinogenic activity of TEA upon a marginal increase in the renal tubule cell adenomas for the male rat which occurred only in the mid dose group (63 mg/kg/day). Tumor incidence in single sections of kidneys for this dose group was 8% which was outside the historical control range of 0%-6% and approached statistical significance in the Fisher exact test (p=0.0560) with the significance of the logistic regression being p=0.060. The incidence in the total sections of kidneys for this dose group was 12% which also approached statistical significance in the Fisher exact test and logistic regression (p=0.053 and p=0.054, respectively). There was no treatment related effect reported for hyperplasias. The number of hyperplasia reported was 1, 0, 1, and 1 in single sections, 8, 8, 6, and 5 in step sections and 9, 8, 7, and 6 in total sections for 0, 32, 63, and 125 mg/kg/day dose groups, respectively.

The incidence of kidney tubule adenoma in single sections was not statistically significant but did suggest the possibility of an effect. The number of adenomas were 0, 1, 4, and 2 for the 0, 32, 63, and 125 mg/kg/day dose groups, respectively. To confirm or reject the possibility of a treatment related effect, the kidneys were further examined with multiple step sections in each kidney. This additional data showed no indication of an effect. The number of adenomas in the step sections were 1, 1, 2, and 2 for 0, 32, 63, and 125 mg/kg/day dose groups, respectively.

A Fisher exact probability test (Siegel, 1956) was conducted to determine if the microscopic evaluation of single and step sections of kidneys were equivalent in the noted incidences of adenomas or hyperplasias relative to the number of sections taken in each case i.e., single or step sections (Table 1). Across all doses, there were a total of 7 adenomas in the single sections versus 6 adenomas in the step sections. The denominator was the total number of sections evaluated from all dose groups which was 398 for single sections and 1592 for step sections. A statistically significant difference was observed between the different hitopathological evaluations (p=0.0068). Fewer tumors were reported for step sections than were expected considering the number of sections taken. A similar analysis was also conducted on the incidence of kidney adenomas reported for just the 63 mg/kg/day dose group (Table 1). In this instance, 4 tumors were reported in 98 single sections versus 2 tumors in 392 step sections. Again, there was a statistically significant difference (p=0.0163) between the two evaluations with fewer than expected adenomas found in the step sections. In contrast, analysis of the incidence of hyperplasia reported in single versus step sections in all dose groups revealed no statistical difference (p=0.1208).

Table 1

Fisher Exact Probability Test Comparing Single to Step Sections for Number of Adenomas or Hyperplasias Found in reference to Number of Step Sections Taken

Lesion	# Lesions/ # Single Sections	# Lesions/ # Step Sections	Dose Group	Fisher Exact Probability
Adenoma	7/398	6/1592	All	0.0068*
Adenoma	4/98	2/392	63 mg/kg/day	0.0163*
Hyperplasia	3/398	27/1592	All	0.1208

* Significant at alpha=0.05, one-sided

The incidence of proliferative lesions (adenomas and hyperplasias) in the single, the step, and the total sections were also analyzed by the Cochran-Armitage trend test as shown in Table 2 and the Fisher exact test as shown in Table 3. There were no significant trends and no significant differences between the treated and the control groups, nor did any differences even approach significance. This endpoint had similar results across all dose groups (10, 8, 11, 8 for the 0, 32, 63, and 125 mg/kg/day dose groups, respectively). This similarity, as opposed to adenomas, is due to the number of hyperplasias being greater for the controls in the total sections (9, 8, 7, and 6 for 0, 32, 63, and 125 mg/kg/day dose groups, respectively).

Table 2

Cochran-Armitage Trend Test Results

Section and Lesion	# Lesions for dose groups (mg/kg/day) 0	32	63	125	Trend P-value
Single Proliferative Lesions	1	1	5	2	0.2834
Step Proliferative Lesions	9	8	6	6	0.3304
Total Proliferative Lesions	10	8	11	8	0.8190

Table 3

Fisher Exact Probability Test Results for Comparisons to Control

Dose (mg/kg/day) that Control is Compared To, Section & Lesion	Control Group: # Lesions/ # Animals	Individual Dose Group: # Lesions/ # Animals	Fisher Exact Probability
32, Single Proliferative Lesions	1/50	1/50	0.7525
63, Single Proliferative Lesions	1/50	5/49	0.0976
125, Single Proliferative Lesions	1/50	2/50	0.5000
32, Step Proliferative Lesions	9/50	8/50	0.5000
63, Step Proliferative Lesions	9/50	6/49	0.3030
125, Step Proliferative Lesions	9/50	6/50	0.2883
32, Total Proliferative Lesions	10/50	8/50	0.3976
63, Total Proliferative Lesions	10/50	11/49	0.4791
125, Total Proliferative Lesions	10/50	8/50	0.3976

The data from Dr. Swenberg's re-evaluation of the male rat kidneys were also analyzed. No statistically significant trends (Table 4) or statistical differences from controls (Table 5) were found in the incidence of adenoma, hyperplasias or combined proliferative lesions. NTP also reported no significant trends or differences from controls at the significance level of alpha=0.05. The difference between the 63 mg/kg/day dose and the control group for incidence of adenoma in single sections approached statistical significance in both the NTP and Swenberg data (p=0.056). In contrast, the difference between the treated group and controls in incidence of adenoma for total sections in the Swenberg data did not approach significance (p=0.175). Note the difference in number of total adenomas for Swenberg (1, 3, 4, and 4 for the 0, 32, 63 and 125 mg/kg/day dose groups, respectively) and that of NTP (1, 2, 6, and 4 for 0, 32, 63 and 125 mg/kg/day dose groups, respectively).

Table 4

Cochran-Armitage Trend Test Results for Swenberg Re-read Data

Section and Lesion	# Lesions for dose (mg/kg/day)				Trend P-value
	0	32	63	125	
Single Hyperplasia	1	1	1	1	0.9964
Step Hyperplasia	8	8	7	5	0.3697
Total Hyperplasia	9	8	7	6	0.3838
Single Adenoma	0	1	4	2	0.1207
Step Adenoma	1	2	0	2	0.8358
Total Adenoma	1	3	4	4	0.1812
Single Proliferative Lesions	1	2	5	2	0.3809
Step Proliferative Lesions	9	8	7	6	0.3838
Total Proliferative Lesions	10	9	11	8	0.7591

Table 5

Fisher Exact Probability Test Results for Comparisons to Control for Swenberg Re-read Data

Dose (mg/kg/day) that Control is Compared To, Section & Lesion	Control Group: # Lesions/ # Animals	Individual Dose Group: # Lesions/ # Animals	Fisher Exact Probability
32 Single Hyperplasias	1/50	1/50	0.7525
63 Single Hyperplasias	1/50	1/49	0.7475
125 Single Hyperplasias	1/50	1/50	0.7525
32 Step Hyperplasias	8/50	8/50	0.6071
63 Step Hyperplasias	8/50	7/49	0.5171
125 Step Hyperplasias	8/50	5/50	0.2768
32 Total Hyperplasias	9/50	8/50	0.5000
63 Total Hyperplasias	9/50	7/49	0.4100
125 Total Hyperplasias	9/50	6/50	0.2883
32 Single Adenomas	0/50	1/50	0.5000
63 Single Adenomas	0/50	4/49	0.0563
125 Single Adenomas	0/50	2/50	0.2475
32 Step Adenomas	1/50	2/50	0.5000
63 Step Adenomas	1/50	0/49	0.5051
125 Step Adenomas	1/50	2/50	0.5000
32 Total Adenomas	1/50	3/50	0.3087
63 Total Adenomas	1/50	4/49	0.1748
125 Total Adenomas	1/50	4/50	0.1811

Table 5 (cont.)

Fisher Exact Probability Test Results for Comparisons to Control for Swenberg Re-read Data

Dose (mg/kg/day) that Control is Compared To, Section & Lesion	Control Group: # Lesions/ # Animals	Individual Dose Group: # Lesions/ # Animals	Fisher Exact Probability
32 Single Proliferative Lesions	1/50	2/50	0.5000
63 Single Proliferative Lesions	1/50	5/49	0.0976
125 Single Proliferative Lesions	1/50	2/50	0.5000
32 Step Proliferative Lesions	9/50	8/50	0.5000
63 Step Proliferative Lesions	9/50	7/49	0.4100
125 Step Proliferative Lesions	9/50	6/50	0.2883
32 Total Proliferative Lesions	10/50	9/50	0.5000
63 Total Proliferative Lesions	10/50	11/49	0.4791
125 Total Proliferative Lesions	10/50	8/50	0.3976

Eustis *et al.* (1994) reported the range of incidence of male rat kidney proliferative lesions from 13 NTP studies in which step sections were taken (Eustis *et al.*, see Table 1). For total sections, the range of total tumors was 0% to 16% and for hyperplasias was 0% to 20%. These data provide the historical control data base for studies in which step sections are taken, assuming as the authors did, that the environmental and biological variables that could influence results were limited. The highest incidence of tumors for total sections was 12% in the NTP TEA data for the 63 mg/kg/day dose group and 8% in Swenberg's TEA data for both the 63 mg/kg/day and 125 mg/kg/day dose groups. These values fall within the total section, total tumor historical control range from Eustis *et al.* (1994). The incidence of hyperplasia for total sections in the dosed groups ranged from 16% to 12% for both the NTP TEA data and the Swenberg

TEA data. These values fall within the range of 0% to 20% for the total section, hyperplasia historical controls from Eustis *et al.* (1994).

In summary, the incidence of adenoma in the step sections showed no treatment related effect and was less than expected given the additional sections taken. The incidence of 8% for Swenberg's adenoma total section data in the 63 mg/kg/day dose did not even approach significance. Both the NTP and Swenberg adenoma total section data were in the range of the total section, total tumor historical controls reported by Eustis *et al.* (1994). The total proliferative lesion data displayed no significant trend or differences between treated and control groups of rats as the incidence of these lesions was similar across dose groups.

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REFERENCES

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Siegel, S. (1956). *Non-Parametric Statistics for the Behavioral Sciences*. McGraw-Hill, New York.

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EDUCATION

1960	**High School:** Detroit Lakes, Minnesota
1964	**College:** University of Minnesota, B.S. (Pre-Vet) with high distinction
1966	**Graduate or Professional School:** University of Minnesota, D.V.M.
1968	Ohio State University (Veterinary Pathology) M.S.
1970	Ohio State University (Veterinary Pathology) Ph.D.

PROFESSIONAL CERTIFICATION

Licensed Veterinarian in Ohio and Michigan

Diplomate, American College of Veterinary Pathologists, 1971–

PROFESSIONAL TRAINING

1964	NIH Predoctoral Fellowship, Department of Veterinary Pharmacology, University of Minnesota.
1966-70	NIH Postdoctoral Trainee, Department of Veterinary Pathology, Ohio State University.
1970	Research Associate, Department of Veterinary Pathology, Ohio State University.
1970-72	Assistant Professor (Chief of Applied Pathology), Department of Veterinary Pathology, Ohio State University.
1972	Associate Professor (Chief of Applied Pathology), Department of Veterinary Pathology, Ohio State University.

HONORS

B.S. with high distinction

Phi Zeta

George H. Scott Award – Toxicology Forum

John Barnes Prize Lectureship – British Toxicology Society

PROFESSIONAL SOCIETIES

American Association for the Advancement of Science

American Association for Cancer Research

American Association of Neuropathologists

American College of Veterinary Pathologists

American Society for Investigative Pathology

Society of Toxicologic Pathologists

Society of Toxicology

ADVISORY POSTS

1973	Contract Reviewer for the National Cancer Institute.
1977	Grant Reviewer for the American Cancer Society.
1977	Member of the Education Committee, American College of Veterinary Pathologists.
1977-78	Member of the Chemical Industry Institute of Toxicology Scientific Advisory Panel.
1978-79	Member of the Graduate Advisory Committee, Western Michigan University.
1978-81	NCI Cause and Prevention Scientific Review Committee.
1978	Member of the Duke Comprehensive Cancer Center ALIF Operational Committee.

1972-76	Research Scientist, Pathology & Toxicology Research Unit, The Upjohn Company.
1976-78	Research Section Head, Pathology & Toxicology Research Unit, The Upjohn Company.
1977-78	Research Section Head, Genetic Toxicology, The Upjohn Company.
1978-84	Head, Department of Pathology, Chemical Industry Institute of Toxicology.
1978-89	Adjunct Professor, Department of Pathology, School of Medicine, The University of North Carolina at Chapel Hill.
1979–	Adjunct Associate Professor of Pathology, Duke University Medical Center.
1979–	Graduate Faculty, Department of Pathology, Duke University Medical Center.
1979–	Member, Duke University Comprehensive Cancer Center.
1984-89	Head, Department of Biochemical Toxicology and Pathobiology, Chemical Industry Institute of Toxicology.
1989	Head, Department of Drug Safety Evaluation, Glaxo, Inc.
1989	Visiting Professor, Department of Pathology, University of North Carolina School of Medicine.
1989	Faculty, Curriculum in Toxicology, University of North Carolina at Chapel Hill.
1990	Research Professor, Department of Pathology, University of North Carolina School of Medicine.
1990–	Professor, Department of Environmental Sciences and Engineering, University of North Carolina School of Public Health.
1991–	Professor, Department of Pathology, University of North Carolina School of Medicine.
1991–	Member, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill.
1992–	Director, Curriculum in Toxicology, University of North Carolina at Chapel Hill.

1980-86	Member, National Toxicology Program Board of Scientific Counselors, Panel of Experts.
1981	Grant Reviewer for the National Cancer Institute.
1982-86	Member, National Toxicology Program Board of Scientific Counselors.
1982	Member, Formaldehyde Working Group, International Agency for Research on Cancer.
1983-84	NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation.
1983	Carcinogenicity Panel, Consensus Workshop on Formaldehyde.
1984	Ad Hoc Member – Chemical Pathology Study Section.
1985	Grant Reviewer – Chemical Pathology Study Section.
1985-86	Chairperson, National Toxicology Program Board of Scientific Counselors.
1985-89	Member, Environmental Protection Agency, FIFRA Scientific Advisory Panel.
1986-89	Member, NYU Institute of Environmental Medicine, NIEHS External Advisory Committee.
1986-88	Member, National Science Foundation/Office of Science and Technology Policy Committee to review the Scientific Basis for Risk Assessment Assumptions.
1986	Member, NIH Biomarkers Panel of the Committee to Coordinate Environmental Health Related Programs (CCE HRP) on Toxicity Testing.
1987–	Member, American Health Foundation Scientific Advisory Board.
1987-89	Member, NIEHS Division of Biochemical and Risk Assessment Board of Scientific Counselors.
1987–	Member, Advisory Board, CRC Critical Reviews in Environmental Carcinogenesis.
1987-88	Vice President Elect, Carcinogenesis Specialty Section, Society of Toxicology.
1988-89	Vice President, Carcinogenesis Specialty Section, Society of Toxicology.
1988-90	Member, Awards Committee, Society of Toxicology.

1989-90	President, Carcinogenesis Specialty Section, Society of Toxicology.
1989	Member, Program Committee, American Association for Cancer Research.
1989–	Member, ILSI Health and Environmental Sciences, Board of Trustees.
1990-93	Member, Exhibits Committee, American Association for Cancer Research.
1990–	Member, Public Education Committee, American Association for Cancer Research.
1990–	National Coordinator, State Legislative Committees, American Association for Cancer Research.
1990–	Member, North Carolina State Legislative Committee, American Association for Cancer Research.
1990-91	Member, AAAS-ABA NCLS Task Force on Science and Technology in the Courts.
1991	Chairperson, Carcinogenesis, Program Committee, American Association for Cancer Research.
1991	Member, IARC Working Group on the use of mechanistic data in cancer risk assessment.
1991-92	Vice President, North Carolina Society of Toxicology.
1991-94	Member, Membership Committee, Society of Toxicology.
1992–	Member, ILSI Risk Science Institute, Board of Scientific Directors
1992-93	President, North Carolina Society of Toxicology.
1993–	Member, Board of Scientific Councilors, Division of Cancer Etiology, National Cancer Institute.
1993	Member, IARC working group on the role of IARC in quantitative estimation and prediction of human risks of cancer.
1994–	Council Member, Society of Toxicology.
1994	Member, EPA Workshop on Cancer Risk Assessment Guidelines Issues.

EDITORIAL AND PEER REVIEW EXPERIENCE

Editorial and Editorial Advisory Boards (Current)

Cancer Epidemiology, Biomarkers and Prevention
Cancer Research
Carcinogenesis
CRC Critical Reviews in Environmental Carcinogenesis
Food and Chemical Toxicology
Methods in Toxicology

Editorial and Editorial Advisory Boards (Past)

Chemical-Biological Interactions
Chemical Research in Toxicology
Fundamental and Applied Toxicology
Toxicologic Pathology

Reviewer for:

Biochimica et Biophysica Acta
Cancer Research
Carcinogenesis
Chemico-Biological Interactions
Fundamental and Applied Toxicology
Environmental Research
European Journal of Cancer
Journal of Biological Chemistry
Journal of Neuropathology and Experimental Neurology
Mutation Research
Neurotoxicology
Nucleosides and Nucleotides
Proceedings of the National Academy of Science
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2. Bettison, L. G., J. B. McLaren, F. D. Kirkpatrick and C. C. Melton. 1984. Relationship among live and carcass traits and within class variance in show steers allotted to class by hip height. J. Anim. Sci. 59(Suppl. 1):41.

3. Bettison, L. G., J. B. McLaren and F. D. Kirkpatrick. 1985. Predicting 365-day hip height in performance tested bulls. J. Anim. Sci. 61(Suppl. 1):5.

4. Gollapudi, B. B. , V. A. Linscombe, L. G. McFadden and S. J. Lick. 1994. The *in vitro* rat lymphocyte chromosomal aberration test (RLCAT): background aberration rates over a 5-year period. Environmental and Molecular Mutagenesis 23 (Suppl 23):21.

JAMES G. FOX, DVM
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Harvard, MA 01451

Degrees

DVM Colorado State University, 1968
MS Stanford University, 1972

State Licenses

California, Colorado, Massachusetts

Education

Stanford University, 1970-1973, Medical Microbiology and Laboratory Animal Medicine
Colorado State University, 1964-1968, Veterinary Medicine
University of Nevada, 1962-1964, Preveterinary Medicine
University of Oregon, 1961-1962, Biological Science

Board Certification

American College of Laboratory Animal Medicine, 1974

Awards and Honors

1990 AVMA Charles River Prize in Laboratory Animal Science
1990 Fellow, Infectious Diseases Society of America
1983-84 Certificates of Achievement, American College of Laboratory Animal Medicine
1970-73 NIH Postdoctoral Fellow
1970 Certificate of Achievement, US Army
1964 Alpha Zeta

Professional Experience

1974 - **Massachusetts Institute of Technology**, Cambridge, Massachusetts

- 1988- **Professor and Director**, Division of Comparative Medicine, Whitaker College of Health Sciences
- 1988- **Professor, Division of Toxicology**
- 1983-88 **Professor and Director**, Division of Comparative Medicine; Professor, Applied Biological Sciences
- 1980-83 **Associate Professor** with tenure, Department of Nutrition and Food Science (Department of Applied Biological Sciences)
  Director, Division of Comparative Medicine
- 1975-80 **Associate Professor**, Department of Nutrition and Food Science
  Head, Division of Laboratory Animal Medicine, Department of Medicine
- 1974-75 **Institute Veterinarian** Research Associate, Department of Nutrition and Food Science
  Director, Animal Care Facility

1981- **Tufts University** School of Veterinary Medicine

- 1983- **Adjunct Professor**, Department of Comparative Medicine
- 1981-82 **Adjunct Associate Professor**, Department of Comparative Medicine

1989- **University of Pennsylvania**, School of Veterinary Medicine

- 1989- **Adjunct Professor**, Department of Clinical Studies

1977- **Governmental Committees/Boards**

- 1994- **Member**, Task Force on Long Range Planning for NIH National Center for ResearachResources.
- 1992- **Israel Academy of Sciences and Humanities:** Basic Research Foundation. Metabolism and Biological Effect of B-Carotene Isomers of *Dunaliella-bardawil* (#419/92-17.1).
- 1983- **Ad Hoc Reviewer**, National Institute on Aging
- 1983- **Ad Hoc Reviewer**, National Institute of Child, Health and Human Development
- 1978- **Special Consultant**, EPA Science Advisory Board, Health Effects Research Review Group
- 1978- **Special Consultant**, National Center for Research Resources, Comparative Medicine Program
- 1977- **Special Consultant**, NCI
- 1985 **Member**, Ad Hoc Committee on Selection of Hamsters for Chemical Toxicity and Carcinogenicity Studies, NIEHS
- 1981-85 **Member**, NIH National Center for Research Resources, Comparative Medicine Program, Review Committee Study Section (**Chairman**, 1984-85)
- 1979-82 **Member**, Ad Hoc NCI Construction Review Committee
- 1978-81 **Special Consultant**, Food and Drug Administration
- 1980 **Member**, Ad Hoc NIEHS Committee on Chemical Contaminants in Laboratory Animal Diets

1978- **National Research Council/National Academy of Sciences**

- 1985-88 **Chairman**, Committee for a National Survey of Laboratory Animal Usage, Facilities, and Resources, Commission of Life Sciences
- 1985-89 **Member**, Ad Hoc Subcommittee to Review the Questionnaire
- 1980-82 **Member**, Committee on Veterinary Medical Sciences, Assembly of Life Sciences
- 1978-80 **Member**, Committee on Laboratory Animal Data, Institute of Laboratory Animal Resources

Special Consultancy/Committees/Appointments

Consulting Veterinarian

1994-	Biodevelopment Laboratories
	Tissue Engineering
1991-	Collaborative Biomedical Research Laboratories
	Therion Inc.
	Virus Research Institute
	OraVax, Inc.
1989-93	Alkermes
1987-	Smith College, Amherst MA
1986-91	Oncogene (formerly Applied Biotechnology)
1983-	Boston College
1982-	Beth Israel Hospital (Boston)
1982	Repligen Inc
1979-	Biotek Inc
1978-	IBM, Boulder CO
1974-93	Biodevelopment Laboratories (formerly Arthur D Little, Inc)
1988-92	Organogenesis, Inc.
1985-88	Cambridge Diagnostics Inc
1984-88	Centocor
1980-83	Wellesley College

Special Consultant, Animal Resources and Facility Design, and *In Vivo* Model Development

1995	University of Pennsylvania, Institute for Human Gene Therapy, Philadelphia, PA
1994	Salk Institute, La Jolla, CA
	ITT Research Institute, Chicago, IL
	Wyeth-Ayerst, Princeton, NJ
	Northwestern University, Chicago, IL
	University of Vermont, Burlington, VT
	Glaxo Ltd, United Kingdom
1993	Wyeth-Ayerst, Taplow, United Kingdom
	Merck, Sharp and Dohme Research Laboratories,
	King of Prussia, PA
	Wyeth-Ayerst, Chezy, NY
	New York Medical Center, NYC, NY
	Abbott Labs, Chicago, IL
	National Cancer Center, Frederick, MD
	IIT Research Institute, Chicago, IL
	Salk Salk Institute, LaJolla, CA
	Sandoz Research Institute, Newark, NJ
1992	Merck Sharp and Dohme Research Laboratories, Rahway NJ
	Pfizer Central Research Division, Groton CT
	Parke-Davis Pharmaceutical Research Division,
	Ann Arbor MI
	Schiapparelli Searle, Skokie IL
	American Cyanamid Company, Pearl River NY
	Wyeth-Ayerst, Princeton NJ
	Wyeth-Ayerst, Radnor PA
	Wyeth-Ayerst, Chezy NY

Praxis Biologics, Rochester NY
Salk Institute, LaJolla CA
Hoffmann-LaRoche, Basel, Switzerland

1991 New England Deaconess Hospital, Boston MA
Abbott Laboratories, Research Division, Chicago IL
Albert Einstein College of Medicine, New York, NY
Salk Institute, La Jolla, CA

1990 USDA Nutrition Center, Tufts University, Boston MA
GD Searle Company, Chicago IL

1989 Eunice Shriver Kennedy Center, Waltham MA
University of California, UCLA Harbor Medical Center, Torrance CA
Tufts University, Medford MA
Davy McKee, Berkeley Heights NJ

1988 Long Island Jewish Hospital, Long Island NY
Sandoz Research Institute, Newark NJ

1987 University of Arkansas Cancer Center, Little Rock AR
St Louis Jewish Hospital, St Louis MO
Smith College, Amherst MA
Brown University, Providence RI

1986 Columbia University, New York NY
Travenol Laboratories, Chicago, IL

1985 University of Kansas, Kansas City KS
Tufts University School of Medicine, Boston MA
Cornell University, Ithaca NY

1984 Massachusetts General Hospital, Boston MA
EG&G Mason Research Institute, Worcester MA
Boston University Medical Center, Boston MA

1980 Vanderbilt University, Nashville, Tennessee

Other Professional Experience

1976- **Staff Affiliate, Angell Memorial Hospital, Boston, Massachusetts**

1974- **Director, Animal Care Facility, Research Affiliate in Experimental Pathology - Forsyth Dental Center, Boston, Massachusetts**

1973-74 **Attending Veterinarian, National Jewish Hospital, Denver, Colorado**

1973-74 **Faculty Affiliate, Colorado State University, University of Colorado Medical Center**

1973 **Staff Veterinarian, Stanford University, Division of Laboratory Animal Medicine**

1970-72 **Pathology and Microbiology support, San Francisco Zoological Gardens**

Postdoctoral NIH Fellowship in Laboratory Animal Medicine and Medical Microbiology. Stanford University, Stanford, California

Co-Investigator in research on Oil Exposed Related Mortalities in Waterfowl, funded by grant from Standard Oil Company of California

1968- **Private Practice**. Part-time employment in Maryland, Florida, and California

1968-70 **Veterinarian** in diagnostic and veterinary activities, Laboratory Animal Branch US Army Veterinary Corp, Biological Laboratories, Animal Division, Ft Detrick, Maryland

Professional Associations/Committees

American Academy of Clinical Toxicology

American Association for Accreditation of Laboratory Animal Care
- 1983-85 Member, Executive Committee
- 1983-85 Chairman, Council on Accreditation
- 1977-85 Member, Council on Accreditation
- 1980-82 Vice-Chairman, Council on Accreditation
- 1976- Special Consultant

American Association for Laboratory Animal Science
- 1984 Seminars Chairman, 35th Annual Session of AALAS, Cincinnati OH

American Association for the Advancement of Science

American College of Laboratory Animal Medicine
- 1994- Task Force on ACLAM Training Requirements
- 1990-91 President
- 1989-90 President-elect
- 1989-92 Member, Board of Directors
- 1987-89 Task Force on ACLAM Journal
- 1980-84 Chairman, Laboratory Animal Medicine Text Subcommittee
- 1983- Chairman, Legislative Liaison Committee
- 1982-83 Honorary Diplomate Nomination Committee
- 1978-81 Audit Committee (Chairman, 1981)
- 1980- Publications Committee
- 1978-80 Member, Board of Directors
- 1979 Forum Subcommittee (Biohazards)
- 1978-79 Recruitment and Training Committee
- 1977 Nominating Committee

American College of Toxicology

American Committee on Laboratory Animal Diseases
- 1985- Board of Directors
- 1989-92 President
- 1988-89 President-elect

American Society of Microbiology
- 1993- Chairman, Annual Research Seminar at AALAS

American Veterinary Medical Association

Association for Biomedical Research

International Campylobacter Society

Comparative Gastroenterology Society

HFRS Virus Guideline Committee

Massachusetts Society of Medical Research

1990-93	President
1989-90	President-elect
1988-89	Vice President
1983-	Member, Executive Committee
1983-	Board of Directors
1985-88	Chairman, Animal Research Policy Committee

New England Branch, American Association for Laboratory Animal Science

1983-	(and 1976-79) Member, Board of Directors
1977-78	President

New England Comparative Pathology Colloquy

New England Comparative Medicine Colloquy

New York Academy of Sciences

International Committee on Systematic Bacteriology Subcommittee on *Campylobacter* and Related Bacteria

Membership, Boards of Directors

1976-79	New England Branch, American Association for Laboratory Animal Science
1983-85	American Association for Accreditation of Laboratory Animal Care
1978-80	American College of Laboratory Animal Medicine
1983-86	New England Branch, American Association for Laboratory Animal Science
1983-	Massachusetts Society for Medical Research
1985-	American Committee on Laboratory Animal Diseases
1989-92	American College of Laboratory Animal Medicine
1992-	Public Responsibility in Medicine and Research

MIT Committees

1994-	Committee on the Assessmentof Biohazards
1985-	Premedical Advisory Council
1983-	Faculty Council
1979-	Committee on Toxic Chemicals
1978-87	Committee on the Assessment of Biohazards
1978-87	Council on Environmental Health & Safety
1978-79	Committee on the Use of Humans in Research
1974-	Committee on Animal Care (Chairman, 1974-85)

Member, MIT and Tufts PhD Thesis Committees

Green, Laura C. "Nitrite and Nitrate: Toxicity, Metabolism, and Biosynthesis," MIT, January, 1981.

Brown, Larry R. "Controlled Release Polymers: *In Vivo* Studies of Insulin and Other Macromolecules," MIT, May, 1983.

Salinas, Julio A. "Long Term Evaluation of the Safety and Wholesomeness of a Meat Analogue in Rats," MIT, February, 1983.

Licht, William R. "Modeling and Kinetics of Gastric Nitrosation," MIT, May, 1986.

Yu, Yong-ming. "The Quantitative Role of the Splanchnic Bed in the Economy of Whole Body Leucine Metabolism: Isotopic and Chemical Balance Studies in the Dog," MIT, August, 1987.

Carroll, Rona. "Sex Differences in the Regulation of Luteinizing Hormone Secretion in the Ferret, a Reflex Ovulator," MIT, October, 1987.

Leaf, Cynthia. "Cell Mediated Mechanisms of Endogenous Nitrosation," MIT, April, 1990.

Smith, Jennifer L. "Pharmaco Kinetics of Methylamines," MIT, September, 1992.

Handt, Larry "*Helicobacter pylori* and Gastrospirrulum hominis-like organism infection in Rhesus monkeys," MS University of Pennsylvania, April, 1993.

Jing, Yu. "An Animal Model for Studies of Gastric Cancer," Tufts 1995.

Jackson, Lynn. "Evaluation of Hollow Fiber Bioreactor Systems as an Alternative to Murine Ascites Production for Small Scale (Less than 1 Gram) Monoclonal Antibody Production," MS MIT, 1994.

Lewis, Richard G. "Detection of Human Pathogenic Viruses in Aquatic Environments Using the Polymerase Chain Reaction," MIT 1995.

Andrutis, Karl. "*Helicobacter felis* Infection and Gastric Carcinogenesis in Mice: An animal model for studies of human cancer," MIT (in progress).

Supervisor, Postdoctoral Training Program in Comparative Medicine/Pathology

Steve Niemi, DVM Washington State University; Diplomate ACLAM; completed DCM training program 1985; now Vice President, EG&G Mason Research, Worcester MA.

Mary Ellenberger, MS Iowa State University; DVM Iowa State University, Diplomate ACLAM; completed DCM training program 1986; now Director, Tufts/New England Medical Center, Boston MA; and Adjunct Instructor, Tufts University School of Veterinary Medicine, Grafton MA.

Barbara Garibaldi, DVM Purdue University; Diplomate ACLAM; completed DCM training program 1987; now Clinical Veterinarian, Boston Veterans Administration Hospital, Boston MA; Attending Veterinarian, MIT Division of Comparative Medicine, Cambridge MA; and Adjunct Instructor, Tufts University School of Veterinary Medicine, Grafton MA.

Karen Krueger, MS Mt Holyoke College, DVM Tufts University; Diplomate ACLAM; completed DCM training program 1988; now Director, Children's Hospital, Department of Animal Resources, Boston MA.

Alice Liberson, DVM Michigan State University; Diplomate ACVP; completed DCM training program 1983; now Director of Marketing, Astra Pharmaceuticals, Worcester MA.

Neil Lipman, VMD University of Pennsylvania; Diplomate ACLAM; completed DCM training program in 1986; Director, Animal Resources Center, and Associate Professor, Committee on Comparative Medicine, University of Chicago, Chicago IL.

Joseph Scott, VMD University of Pennsylvania; Diplomate ACLAM; completed DCM training program 1988; now Assistant Professor, Yale University, New Haven CT.

Glen Otto, DVM University of Minnesota; Diplomate ACLAM; completed DCM training program 1990; now Assistant Professor, Stanford University Medical School, Palo Alto CA.

Eva Ryden, PhD, Boston University, DVM Tufts Veterinary School; Diplomate ACLAM; completed DCM training program 1991; now Clinical Veterinarian and Lecturer, Department of Internal Medicine, Division of Medical Genetics and Molecular Medicine, Jefferson University, Philadelphia PA.

Brian Corning, DVM Colorado State University; Diplomate ACLAM; completed DCM training 1991; now Assistant Dirctor, Comparative Research Center, Rush-Presyterian-St Luke's Medical Center, Chicago IL.

Lori Palley, DVM Tufts Veterinary School; completed DCM training program 1991; now Research Scientist, Eli Lily, Indianapolis IN.

Michael Blanco, DVM Iowa State University; Diplomate ACLAM; completed DCM training program 1993; now Chief, Clinical Laboratory Animal Medicine and Instructor, University of Chicago, Committee on Comparative Medicine and Pathology, Chicago IL.

Susan Erdman, MS, Lehigh University, DVM University of Mississippi; MsPH, Harvard School of Public Health; now Research Scientist, Division of Comparative Medicine, MIT, Cambridge MA.

Marisa Esteves, VMD University of Penn.; completed DCM training program 1993; now Instructor, Division of Veterinary Resources, University of Miami, Miami FL.

Richard Hurley, MS, DVM Ohio State University; completed DCM training program 1994; now Assistant Director, Center for Research Animal Resources, Cornell University, and Instructor, State Diagnostic Laboratory, New York State College of Veterinary Medicine, Cornell University, Ithaca NY.

Lynn Jackson, DVM Ohio State University; MS MIT, completed DCM training program 1994. Harvard Medical School, New England Regional Primate Center.

Scott Perkins, MS, VMD, University of Pennsylvania; completed DCM training program 1995; now Clinical Veterinarian, Cornell Medical Center and Sloan-Kettering Research Institute, Ithaca NY.

Karl Andrutis, DVM Tufts Veterinary School; completed DCM training program 1995; continuing PhD program at MIT, Division of Toxicology.

Margaret Batchelder, DVM Tufts Veterinary School; entered DCM training program 1993.

Leslie Coleman, DVM University of California-Davis; entered DCM training program 1994; also enrolled in PhD program, MIT Division of Toxicology.

Nirah Shomer, PhD/DVM Universityof Minnesota; entered DCM training program 1995.

Sonya Pollard, DVM Oregon State University; entered DCM training program 1995.

Kim Saunders, DVM Oregon State University; entered DCM training program 1995.

Reviewer, journals

American Journal of Gastroenterology
American Journal of Pathology
American Journal of Veterinary Research
Canadian Journal of Microbiology
Cancer Epidemiology, Biomarkers and Prevention
Digestive Diseases and Science
Gastroenterology
Infection and Immunity
Infectious Diseases in Clinical Practice

Journal of Clinical Microbiology
Journal of Experimental Pathology
Journal of Experimental Pathology and Environmental Health
Journal of Infectious Diseases
Journal of Nutritional Biochemistry
Journal of the American Veterinary Medical Association
Journal of Wildlife Diseases
Lab Animal
Laboratory Animal Science
Review of Infectious Diseases

Reviewer, prospective publications in biomedical research
Academic Press
CRC Press
National Agricultural Library
WH Freeman & Co.

Editor

Laboratory Animal Science
1982- Associate Editor
1983-86 Editorial Board (Chairman 1985-86)

American Journal of Veterinary Research
1990-92 Editorial Board

Special Reports

Co-author on Arthur D Little Inc Report: US Veterinary Medical Manpower Needs - 1978-1990. JAVMA 173:369-372, August 1978.

Co-author on Specialized Veterinary Manpower needs through 1990. Committee on Veterinary Medical Sciences Commission on Life Sciences, NRC/NAS pp. 198, 1983.

Co-author Comparative Medicine *Bridges to Better Health*, pp. 12, 1994.

U.S. Congressional Testimony

Testimony on Budget Subject, NIH Division of Research Resources, presented before the Labor, Health and Human Services, Education and Related Agencies Appropriations Subcommittee of the US House of Representatives, May 1984.

Testimony on Appropriations for Biomedical Research, NIH Division of Research Resources, Subcommittee on Health and Human Services and Education of the House of Representatives, April 1989.

Testimony on Appropriations for Biomedical Research, NIH Division of Research Resources, Subcommittee on Health and Human Services and Education of the House of Representatives, April 1990.

Patents

Kohn JG, Langer RS, Niemi SM, Fox JG. Biodegradable Polymeric Drug Delivery System with Adjuvant Activity (MIT Case No.4286-86).

Videotape

Fox JG, Moreland AF. Campylobacteriosis in Laboratory Animals. VA-EMI Program Number 8, produced by Learning Resources and Communications, Television Division, J Hillis Miller Health Center, University of Florida, 1983.

Books

Foster HL, Small JD, Fox JG (editors). *The Mouse in Biomedical Research*, Vol. I, "History, Genetics and Wild Mice," Academic Press Inc, New York, 1981.

Foster HL, Small JD, Fox JG (editors). *The Mouse in Biomedical Research*, Vol.II, "Diseases," Academic Press Inc, New York, 1982.

Foster HL, Small JD, Fox JG (editors). *The Mouse in Biomedical Research*, Vol. III, "Normative Biology, Immunology and Husbandry," Academic Press Inc, New York, 1983.

Foster HL, Small JD, Fox JG (editors). *The Mouse in Biomedical Research*, Vol. IV, "Experimental Biology and Oncology," Academic Press Inc, New York, 1982.

Fox JG, Cohen BJ, Loew FM (editors). *Laboratory Animal Medicine*, Academic Press Inc, New York, 1984.

Fox JG. *Biology and Diseases of the Ferret*. Lea & Febiger, Philadelphia, PA., 1988.

Clingerman KJ, Fox JG, Walke M. *Ferrets as Laboratory Animals: A Bibliography*. National Agricultural Library, Beltsville MD, 1991.

James G. Fox, DVM

Publications

Fox JG, Hall WC. Fluke (*Gastrodiscoides hominis*) infection in a rhesus monkey with related intussusception of the colon. JAVMA 157:714-716, 1970.

Wikse SE, Fox JG, Kovatch RM. Candidiasis in simian primates. Lab Anim Care 20:1137-1138, 1970.

Fox JG, Soave OA. Pneumococcic meningoencephalitis in a rhesus monkey. JAVMA 159:1595-1597, 1971.

Fox JG, Ediger RD. Nasal leech infestations in the rhesus monkeys: clinical and pathological features. Lab Anim Sci 195:560-562, 1971.

Fox JG, Wikse SE. Bacterial meningoencephalitis in rhesus monkeys: clinical and pathological features. Lab Anim Sci 21:558-563, 1971.

Herman PH, Fox JG. Panophthalmitis associated with diplococcic septicemia in a rhesus monkey. JAVMA 195:560-562, 1971.

Fox JG, Soave OA. Pneumococcic meningoencephalitis in a rhesus monkey. JAVMA 159:1595-1597, 1971.

Fox JG. Abdominal hernias in the rhesus monkey (*Macaca mulatta*). Lab Anim Sci 21:746-747, 1971.

Hall WC, Kovatch RM, Herman PH, Fox JG. Pathology of measles in rhesus monkeys. Vet Pathol 8:307-319, 1971.

Fox JG, Gutnick MJ. Horner's syndrome and brachial paralysis due to lymphosarcoma in a cat. JAVMA 160:977-980, 1972.

Fox JG, Snyder SB. San Francisco dutch duck plague. Smithsonian Institute Center for Short Lived Phenomena (Cambridge, MA), Annual Report, pages 63-65, 1972.

Campbell LH, Fox JG, Drake DF. Ocular and other manifestations of periarteristis nodosa in a cat. JAVMA 161:1122-1126, 1972.

Fox JG, Diaz JR, Barth RA. Nymphal *Porocephalus clavatus* in the brain of the squirrel monkey, *Saimiri sciureus*. Lab Anim Sci 22:908-910, 1972.

Fox JG, Snyder SB, Reed C, Campbell LH. Malignant ependymona in a cat. J Small Anim Pract 14:23-26, 1973.

Snyder SB, Fox JG. Tuberculin testing in rhesus monkeys (*Macaca mulatta*): a comparative study using experimentally sensitized animals. Lab Anim Sci 23:515-521, 1973.

Snyder SB, Fox JG, Soave OA. Subclinical otitis media associated with *Pasteurella multocida* infections in New Zealand white rabbits (*Oryctolagus cuniculus*). Lab Anim Sci 23:270-272. 1973.

Synder SB, Fox JG, Campbell LH, Tam KF, Soave OA. An epornitic of duck virus enteritis (duck plague) in California. JAVMA 163:647-652, 1973.

Fox JG, Beatty JO. Adrenal insufficiency in the dog: two case reports. J Small Anim Pract 14:167-175, 1973.

Fox JG, Snyder SB, Soave OA. Transmissible drug resistance in enterobacteriaceae isolated from healthy nonhuman primates. Am J Vet Res 34:965-970, 1973.

Fox JG, Snyder SB, Campbell LH. Connective tissue nevus in a dog. Vet Pathol 10:65-68, 1973.

Campbell LH, Fox JG, Synder SB. Ocular bacteria and mycoplasma of the clinically normal cat. Feline Practice 1973:10-12, 1973.

Campbell LH, Snyder SB, Reed C, Fox JG. *Mycoplasma felis* associated conjunctivitis in cats. JAVMA 991-995, 1973.

Snyder SB, Fisk SK, Fox JG, Soave OA. Respiratory tract disease associated with *Bordetella bronchiseptica* infection in cats. JAVMA 1973.

Fox JG, Campbell LH, Reed C, *et al.* Dermatophilosis (cutaneous streptothricosis) in owl monkeys. JAVMA 163:642-644, 1973.

Fox JG, Drake KF. Tuberculin testing in *Macaca* species: evaluation of two tuberculin diluents. Lab Anim Sci 24:763-767, 1974.

Fox JG, Campbell LH, Snyder SB, *et al.* Tuberculous spondylitis and Pott's paraplegia in a rhesus monkey (*Macaca mulatta*). Lab Anim Sci 24:335-339, 1974.

Fox JG, Snyder SB, Schmidt GD, Campbell LH. Infection with the nematode *Streptocara incognita* in the Chilean flamingo. J Wildlife Dis 10:66-69, 1974.

Reed C, Fox JG, Campbell LH. Leukemia in a cat with concurrent *Cladosporium* infection. J Small Anim Pract 15:55-62, 1974.

Burek JD, McElyea U Jr, Fox, JG, Stookey JL. Persistent pupillary membranes in a rhesus monkey. JAVMA 164:719-721, 1974.

Fox JG, Frost WW. *Corynebacterium ulcerans* mastitis in a bonnet macaque (*Macaca radiata*). Lab Anim Sci 24:820-822, 1974.

Fox JG, Campbell LH. Serological survey of toxoplasmosis in selected population of veterinarians in California. Calif Vet J 38:32-35, 1974.

Fox JG, Beatty JO. A case report of complicated diabetes mellitus in a cat. J Am Anim Hosp Assn 11:129-134, 1975.

Fox JG. Transmissible drug resistance in *Shigella* and *Salmonella* isolated from pet monkeys and their owners. J Med Primatol 4:165-171, 1975.

Fox JG, Rohovsky MW. Meningitis Caused by *Klebsiella* spp in two rhesus monkeys. JAVMA 167:634-636, 1975.

Fox JG, Aldrich FD, Boylen GW Jr. Lead in animal food. J Toxicol Environ Health 1:461-467, 1976.

Snyder SB, Fox JG, Campbell LH, Soave OA. Disseminated staphylococcal disease in laboratory rabbits. (*Oryctolagus cuniculus*). Lab Anim Sci 26:86-88, 1976.

Fox JG, Hewes K. *Cheyletiella* infestation in cats. JAVMA 169:332-333, 1976.

Fox JG, Murphy JC, Igras VE. Adverse effects of mouse hepatitus virus on ascites myeloma passage in the BALB/cJ mouse. Lab Anim Sci 27:173-179, 1977.

Rohovsky MW, Fox JG, Chalifoux LV. Benign ovarian tertomas in two rhesus monkeys (*Macaca mulatta*). Lab Anim Sci 27:173-179, 1977.

Sansone EB, Fox JG. Potential chemical contamination of animal feeding studies: evaluation of wire and solid bottom caging systems and gelled feed. Lab Anim Sci 27:457-465, 1977.

Fox JG, Murphy JC, Shalev M. What's your diagnosis? [Diagnosis: sparine induced myositis and neuritis.] Lab Anim 6:15-16, 1977.

Fox JG, Galus CB. *Salmonella*-associated conjunctivitis in a cat. JAVMA 171:845-847, 1977.

Fox JG, Niemi SM, Murphy JC, Quimby FW. Ulcerative dermatitis in the rat. Lab Anim Sci 27:671-678, 1977.

Fox JG. Clinical assessment of laboratory rodents on long term bioassay studies. J Environ Pathol Toxicol 1:199-226, 1977.

Shalev M, Murphy JC, Fox JG. Mycotic enteritis in a chameleon and a brief review of phycomycoses of animals. JAVMA 171:872-875, 1978.

Fox JG,Boylen GW Jr. Analysis of lead in animal feed ingredients. Am J Vet Res 39:167-169, 1978.

Fox JG, Reed C. *Cheyletiella* infestation of cats and their owners. Arch Dermatol 114:1233-1234, 1978.

Murphy JC, Niemi SM, Hewes KM, Zink M, Fox JG. Hematologic and serum protein reference values of the *Octodon degus*. Am J Vet Res 39:713-715, 1978.

Arnold DL, Fox JG, Thibert P, Grice HC. Toxicology studies. I. Support personnel. Food Cosmet Toxicol 16:479-484, 1978.

Fox JG, Murphy JC, Shalev M. Systematic fungal infections in cats. JAVMA 173:1191-1195, 1978.

Fox JG, Murphy JC, Esser RE, *et al.* Tuberculosis outbreak in rhesus monkeys immunosuppressed with antithymocyte globulin. J Med Primatol 7:264-273, 1978.

Fox JG, Beaucage CM. The incidence of *Salmonella* in random-source cats purchased for use in research. J Infect Dis 139:362-365, 1979.

Fox JG, Shalev M, Beaucage CM, Smith M. Congenital entropion in a litter of rabbits. Lab Anim Sci 29:509-511, 1979.

Edwards GW, Fox JG, Policastro P, *et al.* Volatile nitrosamine contamination of laboratory animal diets. Cancer Res 39:1857-1858, 1979.

Beaucage CM, Fox JG. Transmissable antibiotic resistance in *Salmonella* isolated from random-source cats purchased for use in research. Am J Vet Res 40:849-851, 1979.

Edwards GW, Fox JG. Significance of nitrosamines in animal diets. [letter] Science 203:6, 1979.

Fox JG, Arnold DL, Thibert P, *et al.* Toxicology studies. II. The laboratory animal. Food Cosmet Toxicol 17:661-675, 1979.

Galler JR, Fox JG, Murphy JC, Melanson DE. Ulcerative dermatitis in rats with over fifteen generations of protein malnutrition. Br J Nutr 41:611-618, 1979.

Fox, Murphy JC. Cytomegalic virus-associated insulitis in diabetic *Octodon degus*. Vet Path 16:625-628, 1979.

Murphy JC, Fox JG, Shalev M. *Paragonimus westermani* infection in a cynomolgus monkey. JAVMA 175:981-984, 1979.

Beaucage CM, Fox JG, Whitney KM. Effect of long-term tetracycline exposure (drinking water additive) on antibiotic-resistance of aerobic gram-negative intestinal flora of rats. Am J Vet Res 40:1454-1457, 1979.

Fox JG, Newberne PM. Environmental safety and chemical hazards in animal research. Part 1. Lab Anim 8(Nov/Dec):35-51, 1979.

Fox JG. Selected aspects of animal husbandry and good laboratory practices. Clin Toxicol 15:539-553, 1979.

Newberne PM, Fox JG. Nutritional Adequacy and quality control of rodent diets. Lab Anim Sci 30:352-365, 1980.

Fox JG, Helfrich-Smith ME. Chemical contamination of animal feeding systems: evaluation of two caging systems and standard cage-washing equipment. Lab Anim Sci 30:967-973, 1980.

Shalev M, Murphy JC, Fox JG, *et al.* Myxoma of bone in a nonhuman primate. Cancer 45:2573-2582, 1980.

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Newberne PM, Fox JG. "Chemicals and toxins in the animal facility." Institute of Laboratory Animal Resources Symposium on Laboratory Animal Housing. Maryland, 1976.

Fox JG. "Sparine induced myositis and neuritis: What is your diagnosis?" 27th Annual Session of AALAS, Houston TX, 1976.

Fox JG. "Good laboratory practice: Animal testing." 2nd Annual Laboratory Symposium on Industrial Toxicology, University of Mississippi, University MS, 1977.

Murphy JC, Fox JG. "Diabetes mellitus in the *Octodon degus*." University of Connecticut, Department of Pathology, Storrs CT, 1977.

Fox JG. "Chemical carcinogens in the animal diet: Evaluation and safety." Joint Scientific and Technical Symposium on Biohazards and the Laboratory Animal Facilities, sponsored by Delaware Valley and Metropolitan New York Branches of AALAS, 1977.

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Fox JG. "Control of environmental variables in laboratory animal research." Combined Washington DC and Delaware Branches, AALAS, Cockeysville NJ, 1977.

Fox JG. "Entropian in rabbits: What's your diagnosis?" 29th Annual Session of AALAS, New York NY, 1978.

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Fox JG. "Experimental variables in animal research." Ethicon Research Laboratories, NJ 1978.

Fox JG. "Food and water contaminants: Influence on experimental design." University of Alabama, Tuscaloosa AL, 1978.

Fox JG. "Chemical contamination in animal diets." ACLAM Forum, Long Island, 1978.

Fox JG. "Chemical decontamination in carcinogen animal studies." Canadian Association of Laboratory Animal Science ONT, Canada, 1978.

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Fox JG. "Personnel health." Biohazards Forum, ACLAM, Atlanta GA, 1979.

Fox JG. "Health management in the animal facility." Biohazards Forum, ACLAM, Atlanta GA, 1979.

Fox JG. "Chemicals in the animal facility." AALAS Quality Assurance Symposium, Morristown NJ, 1979.

Fox JG. "Sanitation in the animal facility." AALAS Quality Assurance Symposium, Morristown NJ, 1979.

Fox JG. "Tropical rat mite dermatitis in laboratory personnel: What's your diagnosis?" 31st Annual Session of AALAS, Indianapolis IN, 1980.

Fox JG. "Interrelationships of disease and environmental variables in safety evaluation." American College of Veterinary Toxicologists Workshop, Ames IA, 1981.

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Fox JG. "Diseases of laboratory animals." New Mexico Academy for Veterinary Practice, Albuquerque NM, 1981.

Fox JG. "The AAALAC site visit." 32nd Annual Session of AALAS, Salt Lake City UT, 1981.

Ackerman JI, Newcomer CE, Fox JG. "Intestinal carriage of *Campylobacter fetus* subsp. *jejuni*." 33rd Annual Session of AALAS, Washington DC, 1982.

Fox JG. "Behavioral assessment by clinical observation." Gordon Research Conference on Toxicology and Safety Evaluation, New Hampshire, 1982.

Fox JG. "Zoonoses of laboratory rodents and mustelids." 119th Annual Meeting of the AVMA, Salt Lake City UT, 1982.

Fox JG. "Diseases and husbandry of pet ferrets." 120th Annual Meeting of the AVMA, New York NY, 1983.

Fox JG, Ackerman JI, Newcomer CE. "*Campylobacter* associated enteritis in laboratory animals." International Symposium on Laboratory Animal Science, Vancouver BC, Canada, 1983.

Fox JG, Hallett M, Rogers A, Schoene W. "Controlled study of nutritional deficiency and alcohol ingestion in production of peripheral neuropathy." American Association of Electromyography and Electrodiagnosis Annual Meeting, Toronto, ONT Canada, 1983.

Taylor NS, Fox JG, Ackerman JI. "Attachment of human and non-human isolates of *Campylobacter fetus* subsp. *jejuni*." 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas NV, 1983.

Abramson S, Fox J, Wigodsky H. "Institute responsibilities with respect to animal research: the IRB/animal care committee, animal assurances, and facilities maintenance." Meeting on Standards for Research with Animals: Current Issues and Proposed Legislation, Public Responsibility in Medicine and Research Conference (PRIM&R), Boston MA, 1983.

Ackerman JI, Murphy JC, Fox JG. "Serologic response in rats intranasally challenged with *Corynebacterium kutscheri*." 34th Annual Session of AALAS, San Antonio TX, 1983.

Murphy JC, Fox JG, Taylor NS, Moyer CF. "Pathogenesis of *Campylobacter* enteritis in man and animals." 34th Annual Session of AALAS, San Antonio TX, 1983.

Maxwell KO, Wish C, Murphy JC, Fox JG. "Serum chemistry reference values in two strains of Syrian hamsters." 34th Annual Session of the AALAS, San Antonio TX, November 1983.

Fox JG, Ackerman JI, Maxwell KO. "*Campylobacter jejuni* associated diarrhea in juvenile beagle dogs." 34th Annual Session of AALAS, San Antonio TX, 1983.

Fox JG. "AAALAC standards, definitions and policies." 34th Annual Session of AALAS, San Antonio TX, 1983.

Fox JG. "Biology and diseases of pet ferrets." Eastern States Veterinary Association Conference, Orlando FL, 1984.

Fox JG. "Why some research institutions are not AAALAC accredited." 16th Annual Laboratory Animal Medicine Conference, Cincinnati OH, 1984.

Fox JG. "The American Association for the Accreditation of Laboratory Animal Care: Policies and procedures." Meeting of the Philadelphia and Vicinity Laboratory Animal Veterinarians, Philadelphia PA, 1984.

Fox JG. "AAALAC accreditation standards." USDA-Animal Care Training Course on Inspections of Research Facilities, College Park MD, 1984.

Fox JG. "How to gain institutional support." Workshop, *Animals and the Scientist: Institutional Responsibilities*, held on behalf of the Scientists Center for Animal Welfare, Johns Hopkins University, Baltimore MD, 1984.

Fox JG. "Campylobacteriosis in laboratory animals." Comparative Medicine Branch, National Institute of Environmental Health Sciences, Research Triangle Park NC, 1984.

Fox JG. "*Campylobacter* enteritis in dogs mimicking parvovirus infection." 23rd Annual Symposium of the Canadian Association for Laboratory Animal Science, Quebec Quebec, Canada, 1984.

Fox JG, Gall B, Murphy JC, Ackerman JI. "Pathogenesis of cervical lymphadenitis in guinea pigs." 35th Annual Session of AALAS, Cincinnati OH, 1984.

Fox JG, Niemi SM, Brown LR, Langer RS. "A non-inflammatory alternative to Freund's adjuvant." 35th Annual Session of AALAS, Cincinnati OH, 1984.

Fox JG. "*Campylobacter jejuni*: a widespread problem in laboratory animals." Ohio Veterinary Medical Association Annual Convention, Columbus OH, 1985.

Fox JG. "*Campylobacter jejuni*." Ohio Veterinary Medical Association Annual Convention, Columbus OH, 1985.

Fox JG. "*Campylobacter* control in the food chain." Ohio Veterinary Medical Association Annual Convention, Columbus OH, 1985.

Fox JG. "Common zoonoses of pocket pets." Ohio Veterinary Medical Association Annual Convention, Columbus OH, 1985.

Fox JG. "Zoonoses: *Campylobacter jejuni*." Ohio Veterinary Medical Association Annual Convention, Columbus OH, 1985.

Taylor NS, Claps MC, Fox JG. "Phenotypic characteristics of *Campylobacter jejuni/coli* isolated from symptomatic and asymptomatic human and non-human sources." 85th Annual Meeting of the American Society for Microbiology, Las Vegas NV, 1985.

Taylor NS, Ackerman JI, Fox JG. "Adherence to tissue cultured cells of *Campylobacter jejuni/coli* from symptomatic and asymptomatic human and animal sources." Third International Workshop on Campylobacter Infections, p 134, Ottawa ONT, Canada, 1985.

Fox JG, Murphy JC, Taylor NS, *et al.* "Further studies on ferrets as animal models of human campylobacter enteritis." Third International Workshop on Campylobacter Infections, p 140, Ottawa ONT, Canada, 1985.

Fox JG, Hallett M, Nicolosi R, Pezeshpour G. "Controlled study of alcohol toxicity on peripheral nerve in primates." American Association of Electromyography and Electrodiagnosis Annual Meeting, Las Vegas NV, 1985.

Fox JG, Niemi SM, Ackerman JI, Murphy JC. "Comparison of methods for diagnosis of natural *Cornebacterium kutscheri* infection in rats." 36th Annual Session of AALAS, Baltimore MD, 1985.

Fox JG, Edrise BM, Cabot E, *et al.* "Isolation of *Campylobacter*-like organisms from gastric mucosa in the ferret." 36th Annual Session of AALAS, Baltimore MD, 1985.

Fox JG, workshop leader. Workshop, *Grantsmanship.* 36th Annual Session of AALAS, Baltimore MD, 1985.

Fox JG, workshop leader. Workshop, *Barrier Maintenance of Rodents in Multipurpose Facilities.* 36th Annual Session of AALAS, Baltimore MD, 1985.

Fox JG, Bhatt PN. "Vaccines: Current status and future prospects." 36th Annual Session of AALAS, Baltimore MD, 1985.

Fox JG. "Animal care assurances: the regulations and implementations for 1986." Society of Research Administrators Northeast Regional Meeting, New Paltz NY, 1986.

Wishnok JS, Fox JG, Tannenbaum SR. "Nitrosation and nitrosamine metabolism in the ferret." International Agency for Research on Cancer, 9th International Meeting on N-Nitro Compounds, Baden Vienna, Austria, September 1-5, 1986.

Fox JG, chairman. Symposium, *Ferret Biology and Medicine.* AVMA Convention, Chicago IL, 1987.

Fox JG. "Intercurrent disease in the ferret: Impact on toxicological research." 26th Annual Meeting of Society of Toxicology, Washington DC, 1987.

Fox JG, Hotaling L, Connors T, *et al.* "Gastric mucosa in the ferret: Bacteriologic and pathologic findings." IVth International Workshop on Campylobacter Infections, Goteborg, Sweden, 1987.

Fox JG. "Gastric microbiota in other species." *Campylobacter pyloridis* Multidisciplinary Workshop, Keystone CO, 1987.

Fox JG. "The ferret as a possible model for *Campylobacter pylori* infection." *Campylobacter pyloridis* Multidisciplinary Workshop, Keystone CO, 1987.

Fox JG. "Zoonotic disease of lab animals." Lab Animal Medicine Seminar Program, University of Pennsylvania, Philadelphia PA, March 1988.

Fox JG, moderator. "Institutional responsibility versus public accountability in animal care and research." Public Responsibility in Medicine and Research Conference (PRIM&R), Boston MA, March 1988.

Fox JG, Sylvina TJ, Hotaling LC, Mesina JE. "Bleeding techniques and intravenous therapy in ferrets (*Mustela putorius furo*). AVMA Convention, Portland OR, July 1988.

Fox JG. "Diseases of the ferret." Westchester/Rockland Veterinary Medical Association, November 1988.

Fox JG. "Common diseases of the ferret." Virginia Polytechnical Institute, School of Veterinary Medicine, Annual Symposium of Exotic Pet Medicine, Blacksburg VA, December 1988.

Liang-Shang G, Stilwell SW, Wishnok JS, Fox JG, Tannenbaum SR. "NDMA dosimetry in ferrets." Advances in the Biology and Chemistry of N-Nitroso and Related Compounds, Omaha NB, 1988.

Russell RG, Sarmiento JI, Fox JG. "Heterogeneity of *Campylobacter* spp. in laboratory housed primates. Implications for understanding the epidemiology under endemic conditions." ACVP meeting, 1988.

Fox JG. "Fading ferret syndrome and GI diseases." Eastern States Veterinary Conference, Orlando FL, January 14-19, 1989.

Fox JG. "Doctor, can we catch it?: Zoonoses." Eastern States Veterinary Conference, Orlando FL, January 14-19, 1989.

Ryden EB, Licht WR, Cabot E, Adkins D, Fox JG. "Maximal and minimal bile reflux surgically altered ferrets as models for studying gastric nitrite processing and gastric cancer." AALAS, 1989.

Correa P, Cuello C, Fox JG. "Heterogeneity of chronic gastritis: the role of *C. pylori*." Vth International Workshop on Campylobacter Infections, Puerto Vallarta, Mexico, 1989.

Fox JG, Schoeb TR, Zhao Z, Lawson GH. "*Campylobacter* omega antigen associated profliferative bowel disease in rabbits." Vth International Workshop on Campylobacter Infections, Puerto Vallarta, Mexico, 1989.

Fox JG, Maxwell KO, Taylor NS, *et al.* "*Campylobacter upsaliensis* isolated from cats." Vth International Workshop on Campylobacter Infections, Puerto Vallarta, Mexico, 1989.

Fox JG, Adkins JA, Wishnok JS. "Nitrate production by immortalized murine macrophages stimulated with *C. pylori* subsp. *mustelae* and *C. jejuni*." Vth International Workshop on Campylobacter Infections, Puerto Vallarta, Mexico, 1989.

Russell RG, Blaser MJ, Sarmiento JI, Fox JG. "Experimental *Campylobacter jejuni* infection in *Macaca nemestrina*." Vth International Workshop on Campylobacter Infections. Puerto Vallarta, Mexico, 1989.

Leunk R, Williams E, Merritt E, Fox JG, Morgan D. "Comparison of *Campylobacter pylori* and *C. pylori* subsp. *mustelae* isolates." American Society for Microbiology, Annual Meeting, 1989.

Fox JG. "Biology and diseases of the ferret." Lab Animal Medicine Seminar Program, University of Pennsylvania, May 1989.

Fox JG, moderator, panel II. "The IACUC's role in educating institutional staff." Public Responsibility in Medicine and Research Conference (PRIM&R), Boston MA, March 1989.

Ryden EB, Lipman NS, Taylor NS, Rose R, Fox JG. "Non-antibiotic associated *Clostridium difficile* enterotoxemia in Syrian hamsters." AALAS, 1990.

Fox JG. "Biology and diseases of the ferret." Michigan Veterinary Conference, Michigan State College of Veterinary Medicine and the Michigan Veterinary Medical Association, January 1990.

Fox JG. "Ferret diseases: Diagnosis and treatment of lab animal diseases." Avian/Exotics Club, School of Veterinary Medicine, University of California, January 1990.

Fox JG. "Biology and diseases of the ferret." Mile High Branch of AALAS, April 1990.

Fox JG. "Zoonotic diseases of laboratory animals." Lab Animal Medicine Seminar Program, University of Pennsylvania, May 1990.

Fox JG. "Gastric *Helicobacter* sp., a new pathogen in man and animals." MD Anderson Cancer Center, Visiting Lecture Series, University of Texas, August 1990.

Fox JG. "*Helicobacter felis* in the germfree mouse and rat." Workshop, *Laboratory Models of Helicobacter pylori Infection*, AB Hassle, Gothenburg, Sweden, May 22, 1990.

Fox JG. "*Helicobacter mustelae* in the ferret." Workshop, *Laboratory Models of Helicobacter pylori Infection*, AB Hassle, Gothenburg, Sweden, May 22, 1990.

Fox JG, Lee A, Otto G, Murphy JC. "Colonization of germ-free rats with gastric spirilla *Helicobacter felis* mimics *Helicobacter pylori* gastritis." American Society for Microbiology Meeting, 1990.

Fox JG. "Diseases of ferrets: Part I and Part II. Small Animal Session, 91st Penn Annual Conference-School of Veterinary Medicine, University of Pennsylvania, January 23, 1991.

Fox JG, G Otto, NS Taylor, *et al.* "*Helicobacter mustelae* gastritis in ferrets as a model of *Helicobacter pylori* gastritis in man." American Gastroenterology Association Meeting, New Orleans LA, 1991.

Dunn B, Sung C, Taylor NS, FoxJG. "Characterization of the urease of *Helicobacter mustelae*." American Society for Microbiology Meeting, 1991.

Seymour C, Kim M, Paster BJ, Dewhirst FE, Fox JG. "*Helicobacter, Campylobacter, Yersinia, Budvicia,* and *Giardia* from mammal and bird feces." American Society for Microbiology Meeting, 1991.

Fox JG. "IACUC 'Hot Spots': Immunological techniques – Monoclonal antibodies, the use of growth factors, and Freund's adjuvant." Public Responsibility in Medicine and Research, Conference (PRIM&R), Boston MA, 1991.

Ryden EB, Marini RP, Rosenblad WD, Murphy JC, Fox JG. "Blood glucose and insulin levels in ferrets treated surgically for pancreatic insulin secreting tumor." AVMA, 1991.

Palley LS, Fox JG, Fuhrman J, *et al.* "The kinetics of the appearance of hypodense eosinophils in the peripheral blood of ferrets experimentally infected with *Brugia malayi*." AALAS, Buffalo NY, 1991.

Fox JG. "Clinical medicine of ferrets as pets [Parts I and II]." Short Course on Military Veterinary Medicine, Walter Reed Army Institute of Research, Washington DC, April 1991.

Fox JG. "Clinical medicine of ferrets as laboratory animals [Parts I and II]." Short Course on Military Veterinary Medicine, Walter Reed Amry Institute of Research, Washington DC, April 1991.

Fox JG. "*Helicobacter* induced duodenal disease in humans and animals." Pfizer Center Research, Groton CT, April 1991.

O'Rourke J, Lee A, Fox JG. "The role of adhesion of *Helicobacter pylori* to gastric epithelium in the pathogenesis of gastroduodenal disease." International Symposium on *Helicobacter pylori* and its Diseases, Tokyo Japan, May 1991.

Soman NR, Fox JG, Murphy JC, Wogan GN. "Expression of the rearranged TPR-MET oncogene in ferret gastric lesions: an animal model study." Annual meeting on Oncogenes, Frederick MD, June 1991.

Fox JG. "Use of ferrets in biomedical research," Tri-Branch AALAS Symposium, Philadelphia PA, June 5, 1991.

Eaton KA, Radin MJ, Fox JG, *et al.* "'*Helicobacter acinonyx*,' a new species of *Helicobacter* isolated from cheetahs with gastritis," International Workshop on *Campylobacter*, *Helicobacter* & Related Organisms, Sydney, Australia, October 7-10, 1991.

Bär W, Enss ML, Hasubski T, Cavalioglu P, Glenn-Calvo E, Hartmann M, Taylor NS, Fox JG. "Adhesion of *Campylobacter jejuni*: a comparison of different methods," International Workshop on *Campylobacter*, *Helicobacter* & Related Organisms, Sydney Australia, October 7-10, 1991.

Fox JG, Taylor NS, Yan L-L, *et al.* "*H. mustelae* isolation from feces of ferrets: Evidence to support fecal-oral transmission of gastric *Helicobacter* sp.," International Workshop on *Campylobacter*, *Helicobacter* & Related Organisms, Sydney, Australia, October 7-10, 1991.

Paster BJ, Dewhirst FE, Seymour C, Fraser GJ, Fox JG. "*Helicobacter* species isolated from bird and swine feces," International Workshop on *Campylobacter*, *Helicobacter* & Related Organisms, Sydney Australia, October 7-10, 1991.

Fox JG, Stills H, Paster BJ, *et al.* "Localization of *Chlamydia* sp. strain SFPD in CLO associated proliferative intestinal tissue of animals by FA monoclonal antibody and *in situ* DNA hybridization," International Workshop on *Campylobacter*, *Helicobacter* & Related Organisms, Sydney Australia, October 7-10, 1991.

Stills H, Fox JG, Paster BJ, Dewhirst FE. "A 'new' *Chlamydia* sp. strain SFPD isolated from transmissible proliferative ileitis in hamsters," International Workshop on *Campylobacter*, *Helicobacter* & Related Organisms, Sydney Australia, October 7-10, 1991.

Lee A, Rune S, Fox JG, *et al.* "Peptic ulcer disease and *Helicobacter pylori*: the role of omeprazole on healing and eradication," International Workshop on *Campylobacter*, *Helicobacter* & Related Organisms, Sydney Australia, October 7-10, 1991.

Fox JG. "Gastric Helicobacters as a cause of gastroduodenal disease in man and animals," Comparative Pathology Seminar Series: College of Agriculture and Natural Resources, University of Connecticut - Storrs, February 13, 1992.

Fox JG. "Development and Review of Occupational Safety and Health Programs for Institutions" (Series C Workshop); and "Review and Assessment of an Individual's Concerns at the Institution: 'Whistle Blower, Procedures" (Series D Workshop);. Public Responsibility in Medicine and Research Conference (PRIM&R), Boston, MA. March 19-20, 1992.

Fox JG. "Helicobacter species induced gastroduodenal disease in man and animals," ASM *Helicobacter pylori* Meeting. University of Connecticut in Hartford. April 24, 1992.

Fox JG. "Biology and diseases of the ferret," University of Maryland, Baltimore, MD. April 1992.

Fox JG. "Animal models of *Helicobacter pylori* infection," Praxis Biologics, Rochester, NY. June 1992.

Fox JG. "*Helicobacter* induced gastroduodenal disease," Merck Sharp and Dohme Research Laboratories. Rahway, NJ. June 1992.

Fox JG. "*Helicobacter* species as a cause of gastroduodenal disease," Parke-Davis Pharmaceutical Research Division, Ann Arbor, MI. July 1992.

Fox JG. "Biology and diseases of the ferret," presented to the New York Veterinary Group, Tarrytown NY, October 1992.

Fox JG. "The ferret as an animal model with naturally occurring *Campylobacter/Helicobacter*," AALAS Annual Meeting, November 1992.

Fox JG. "Careers in comparative medicine," AALAS Annual Meeting, November 1992.

Fox JG. "Animal Model Development for *Helicobacter* - Associated Gastrointestinal Disease," Trans-NIH Coordinating Committee for Research Animal Resources Meeting. December 1992.

Fox JG. "The feasibility of *Helicobacter pylori* vaccine," Merck Sharp and Dohme Research Laboratories, W. Point, PA, January 1993.

Fox JG. "Biology and Diseases of the Ferret," Univ of Pennsylvania seminar program in laboratory animal medicine. April 1993.

Fox JG. "The Importance of Institutional Support," AAAS '93 Symposium, February 12, 1993

Fox JG. "Laboratory Animal Zoonoses," Veterinary Public Health course. Tufts Veterinary School, 1993.

Fox JG. "*Helicobacter mustelae* associated gastritis in the ferret: A model to study *H. pylori* pathology and epidemiology," New Directions in *Helicobacter* Therapy Conference-Glaxo Pharmaceuticals, March 18, 1993.

Fox JG. "Pathogenesis of Campylobacter and Helicobacter," symposium, 93rd General Meeting of the American Society for Microbiology, Atlanta GA, May 20, 1993.

Fox JG. "Biology and Diseases of the Ferret," Maryland Medical Laboratories, Inc., Exotic Animal Conference, Baltimore, MD, June 10, 1993.

Fox JG. "Liver Toxicity in mice at Frederick Cancer Research and Development Center," National Cancer Institute, Frederick, MD, July 14, 1993.

Fox JG. "The ferret as a model to study *Helicobacter* associated gastric carcinogenesis," The 6th International Symposium on *Helicobacter pylori* and its Diseases, Tokyo, Japan, Sept. 16, 1993.

Fox JG. "Limited DNA sequence diversity of *Helicobacter mustelae*, a gastric pathogen of ferrets," Helicobacter and Campylobacter - VIth Workshop on Gastroduodenal Pathology and Helicobacter Pylori, Brussels, Belgium, Sept. 24, 1993.

Fox JG. "Identification of the uncultured intracellular campylobacter-like organism (ICLO) in proliferative bowel disease of ferrets and hamsters," Helicobacter and Campylobacter - VIth Workshop on Gastroduodenal Pathology and Helicobacter Pylori, Brussels, Belgium, Sept 24, 1993.

Fox JG. "Initial isolation and characterization of *Helicobacter mustelae* from the stomach of mink (*Mustelae vision*)," Helicobacter and Campylobacter - VIth Workshop on Gastroduodenal Pathology and Helicobacter Pylori, Brussels, Belgium, Sept 24, 1993.

Fox JG. "*In vivo* models of gastric *Helicobacter* infections," Hunt Helicobacter Conference, Amelia Island, FL., Nov. 4, 1993.

Fox JG. "Antigenic specificity, morphological and molecular characteristics of *Chlamydia trachomatis* strain SFPD, isolated from proliferative ileitis in hamsters," AALAS, Nashville, TN, Nov. 15, 1993.

Fox JG. "*Helicobacter* as an emerging pathogen," presented at Frederick Cancer Research and Development Center, Frederick, MD., November 30, 1993.

Fox JG. "Animal models of *H. pylori*," presented at Harvard Digestive Diseases Center, December 1, 1993.

Fox JG. "The genus *Helicobacter* species: an emerging pathogen," presented at the Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital, February 1, 1994.

Fox JG. "*Helicobacter mustelae* Associated Gastric Disease in the Ferret," presented at the IBC Helicobacter Pylori & Gastroduodenal Disorders Conference, Philadelphia, PA, April 11-12, 1994.

Handt LK, Fox JG, Dewhirst FE, Paster BJ, Yan L, Rufo R. "*Helicobacter pylori* isolated from the domestic cat: public health implications," presented at the American Gastroenterological Association, New Orleans, May 17, 1994.

Palley LS, Murphy JC, Yan L, Taylor NS, Polidoro DP, Fox JG. "Duodenal ulcers associated with *Helicobacter mustelae* immunization of ferrets," presented at the American Gastroenterological Association, New Orleans, May 18, 1994.

Fox JG. "*Helicobacter hepaticus* infection in mice," lecture for the Harvard Medical School Center for Animal Resources and Comparative Medicine, Cambridge, MA, May 27, 1994.

Fox J. "Various species of *Helicobacter*," presented at a meeting of the National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis, Bethesda, MD, May 31, 1994.

Fox JG. "Various species of *Helicobacter*," The Toxicology Forum, 1994 Annual Summer Meeting, Apen CO, July 11-15, 1994.

Palley LS, Fox JG. "The ferret," presented at the New York Veterinary Medical Society, New York NY, September 22, 1994.

Foxall P, Bauerfeind P, Hollingshead M, Fox J, Mobley, H. "PCR amplification of urease gene sequences from *Helicobacter hepaticus*, a newly described pathogen of mice," presented at the VIIth Workshop on Gastroduodenal Pathology and Helicobacter pylori, Houston TX, September 30, 1994.

Fox JG, Goddard PH, Hoffman J, Parsonnet J, Sonnenberg A. "*Helicobacter pylori*: for the clinician," presented by Tufts University School of Medicine and St. Elizabeth's Medical Center of Boston, Boston MA, October 29, 1994.

Fox JG. "*H. pylori*: Model of IBD", presented at the "Genetic Models of IBD", Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital, Boston, MA, November 11-12, 1994.

Fox JG. "*H. pylori* transmission: Environmental sources", presented at the Glaxo Roundtable Conference "Epidemiology of *H. pylori* infection", Brocket Hall, United Kingdom, December 13-14, 1994.

Fox JG. "*Helicobacter pylori*", presented at the MIT Medical Department, Cambridge, MA, January 19, 1995.

Fox JG. "Intestinal Helicobacters", presented at the Crohn's & Colitis Foundation of America "Interactions between Genetics and Microbiology in IBD", Hilton Head, SC, March 4, 1995.

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JAMES G. FOX - CURRENT ACTIVE SUPPORT

a. Source and identifying number: NCI 5-P01-CA26731
PI: Steven Tannenbaum
Title: Endogenous Nitrite Carcinogenesis in Man
b. Your role on project (% effort): Principal Investigator Core 2 and Project 3 (10%)
c. Dates and costs of entire project: 3/1/94-12/31/98 $5,345,174 ($3,736,501 direct)
d. Dates and costs of current year: 1/1/95-12/31/95 $1,016,128 ($707,728 direct) Project 3 and Core 2 $107,067 ($70,439 direct)
e. Specific aims of project: To investigate the role nitrite and N-nitroso compounds play in the etiology of human cancer; to use murine models to study endogenous reactions.
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, %
effort, aims, etc.): None

a. Source and identifying number: NIH RR07989
PI: James G. Fox
Title: Developing and Improving Institutional Animal Resources
b. Your role on project (% effort): Principal Investigator (5%)
c. Dates and costs of entire project: 10/1/92-9/30/95 $148,345 direct
d. Dates and costs of current year: 10/1/94-9/30/95 $80,043 direct
e. Specific aims of project: Renovations in the animal facilities and purchase of equipment.
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

a. Source and identifying number: Oravax, Inc.
PI: James G. Fox
Title: *Helicobacter pylori urease* oral vaccine
b. Your role on project (% effort): Principal Investigator (2.5%)
c. Dates and costs of entire project:
Dates and costs of current year: 1/1/95-6/30/95 $37,328 ($24,558 direct).
e. Specific aims of project: To test the efficacy of an *H. pylori urease* vaccine in cats challenged with *H. pylori*
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, %
effort, aims, etc.): None

a. Source and identifying number: NCI 7S-1716
PI: James G. Fox
Title: *Helicobacter Hepaticus* Associated Active,
Chronic Hepatitis: Diagnosis, Pathogenesis, and Epidemiology.
b. Your role on project (% effort): Principal Investigator (10%)
c. Dates and costs of entire project: 8/1/93-7/30/95 $145,622 ($93,347 direct)
d. Dates and costs of current year: 8/1/94-7/30/95 $76,880 ($50,579 direct)
e. Specific aims of project: To study a new disease characterized by active chronic hepatitis and apparantly caused by a new *Helicobacter* species.

f. Describe scientific and budgetary overlap: None of the studies in this proposal or pending proposals will be undertaken on this contract.
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

a. Source and identifying number: NIH - DK 43406
Subcontract from Boston University
PI: David Cave
Title: Interaction of Helicobacter pylori and gastric epithelia.
b. Your role on project (% effort): Principal Investigator (5%)
c. Dates and costs of entire project: 12/1/93-11/30/96 $299,902 (direct)
d. Dates and costs of subcontract: 12/1/95-11/30/96 $18,723 ($11,557 direct)
e. Specific aims of project: To examine a putative inhibitory protein of parietal cell acid secretion.
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

a. Source and identifying number: CA62520-01
PI: Richard Hynes
Title: Extramural Research Facilities Construction Projects
b. Your role on project (% effort): Co-Principal Investigator (5%)
c. Dates and costs of entire project: 04/15/94-01/30/95 $412,417(direct)
d. Dates of current year: 01/30/95-4/15/96
e. Specific aims of project: To renovate the animal holding facilities in Buildings E17 and E18.
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

a. Source and identifying number: Glaxo, Inc.
PI: James G. Fox
Title: Eradication of *H.mustelae* from ferrets
b. Your role on project (% effort): Principal Investigator (5%)
c. Dates and costs of entire project: 08/01/94-10/30/94 $184,651 ($118,742 direct)
d. Dates and costs of current year: 08/1/94-7/30/95 $127,724 ($82,402 direct)
e. Specific aims of project: To test *in vivo* anti-*Helicobacter* compounds.
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

a. Source and identifying number: NIH P01 HL-4148
PI: Robert Rosenberg
Title: Transgenic Animals - Core Project of Program of Excellence in Molecular Biology
b. Your role on project (% effort): Co-Investigator (10%)
c. Dates and costs of entire project: 10/30/88-11/30/95 $16,561,404 ($10,481,900 direct)

g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

a. Source and identifying number: NCI CA-28842

JAMES G. FOX - PENDING SUPPORT

Subcontract from Louisiana State University
PI: Dr. Pelayo Correa
Title: Etiologic studies of Gastric Carcinoma

b. Your role on project (% effort): Principal Investigator (10%)
c. Dates and costs of entire project: 12/1/95-11/30/96 $891,240 ($586,342 direct)
d. Dates and costs of current year subcontracts: N/A
e. Specific aims of project: To continue to study *H. pylori* infection in a well characterized population in Columbia, to determine transmission routes for *H. pylori* infection and reasons for treatment failures.
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None.

a. Source and identifying number: NIH T32 RR07036
PI: James G. Fox
Title: Postdoctoral Training Program Laboratory Animal Medicine
b. Your role on project (% effort): Principal Investigator (5%)
c. Dates and costs of entire project: 7/1/93-6/30/98 $1,391,147 ($1,322,051 direct)
d. Dates and costs of current year: 7/1/94-6/30/95 $156,230 ($146,654 direct)
e. Specific aims of project: Train veterinarians for careers in biomedical research
f. Describe scientific and budgetary overlap: No overlap
g. Describe adjustments you will make if the present application is funded (budget, % effort, aims, etc.): None

Attachment #4

CHEMICAL MANUFACTURERS ASSOCIATION

DEA NTP STUDY

Position Statement of the CMA Alkanolamines Panel

May 7, 1996

The Alkanolamines Panel of the Chemical Manufacturers Association (CMA) submitted preliminary findings of a life-time toxicology study with diethanolamine (DEA) conducted in male and female mice by the National Toxicology Program (NTP) to the Environmental Protection Agency (EPA) on May 3, 1996. The submission was based on a preliminary pathology report released by NTP.

The preliminary report by NTP indicated that exposed mice showed an increased incidence of liver tumors in males and females, and an increase in kidney tumors in males only, relative to unexposed study mice. The study mice were dosed at levels that were significantly higher, and the number of doses applied to these mice far greater than those that would be anticipated for human exposure.

Similar results were not reported in a parallel rat NTP study with DEA.

Submission of new toxicology findings on chemicals is required under Toxic Substances Control Act (TSCA) Section 8(e), whether the findings are substantiated or not. The NTP report is interim and preliminary in nature. No detailed data have been made available, nor statistical evaluations conducted. Further evaluation is essential to interpret these data, and to reach any conclusions based upon the study.

Additional evaluation is also essential to determine the presence or absence of a bacterial infection in the study mice. A specific bacteria, *Helicobacter hepaticus*, can infect the livers of mice, and this infection is known to cause cancer. While the NTP interim report on DEA stated that *Helicobacter hepaticus* was not present in the study mice, NTP may not have utilized techniques recently developed by the Massachusetts Institute of Technology (MIT) to specifically identify this bacteria, when other techniques have failed to do so.

The Alkanolamines Panel strongly believes that further evaluation of the NTP study methodology and findings must be conducted before any relevant conclusions regarding the health and safety aspects of DEA can be reached based on this study.

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