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

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

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

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

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

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

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

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

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

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

hematocrit, increased in reticulocyte production, splenomegaly, and increased Heinz body formation were seen in rats and mice of both sexes exposed to MB. Histologically, there was hyperplasia of the bone marrow in response to the anemia.

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

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

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

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

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

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