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WILMINGTON, DELAWARE

PETROCHEMICALS DEPARTMENT

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PLAINTIFF'S EXHIBIT DUP-1676

November 8, 1978

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THIS COPY FOR

The last pg, Appendix A, tells it all.
WTZ

FROM: W. M. BRANAN

SHORT-TERM ASSAYS FOR IDENTIFYING POTENTIAL CARCINOGENS AND MUTAGENS

Follow-up of Positive Assay Results

Ref.: C. F. Reinhardt's Memo to Haskell Laboratory Liaison Committe, 11/2/78

The attached memo gives Haskell's procedure for following up positive mutagen tests. This has been approved by the EQC. The Appendix A (the last page) is the actual procedure.

WMB:svw

att.

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INCORPORATED
WILMINGTON, DELAWARE 19898
CENTRAL RESEARCH & DEVELOPMENT DEPARTMENT

HASKELL LABORATORY
FOR
TOXICOLOGY AND INDUSTRIAL MEDICINE

cc: Environmental Quality Committee
T. L. Cairns/M. S. Sadler
B. C. McKusick
J. G. Aftosmis/D. F. Krahn

November 2, 1978

MEMO TO: HASKELL LABORATORY LIAISON COMMITTEE

FROM: C. F. REINHARDT, M. D. CFR

SHORT-TERM ASSAYS FOR IDENTIFYING POTENTIAL CARCINOGENS AND MUTAGENS

Follow-up of positive assay results

Short-term or predictive assays are being used to indicate the likelihood that a chemical is a potential carcinogen or mutagen for humans. The majority of these assays measure mutation* or DNA damage. An effect in non-mammalian organisms or cultured mammalian cells may indicate a potential mutagenic hazard for humans, since the structure of DNA is basically the same in all organisms. Also, a potential carcinogenic hazard may be identified since the induction of cancer by many chemicals is thought to involve a mutagenic event. Although the present day predictive assays are useful for identifying chemicals that may be hazardous, the data that is obtained from them is not sufficient for concluding that the chemical will cause cancer or be mutagenic in humans. The most definitive, although not absolute, means to identify carcinogens is to evaluate the effect of chemicals in animals.

At Haskell Laboratory, two predictive assays are available for routine use. They are the Ames assay and the Chinese Hamster Ovary cell (CHO) assay. Other assays will be made available at Haskell as their value is demonstrated.

*A mutation is a stable alteration in the genetic material (the DNA) of a cell that is inherited when the cell divides. Mutations can be passed on to future generations if they occur in the cells involved in the reproduction of the organism (the germ cells) or they may die with the host if they occur in the cells of the organism that are not involved in reproduction (the somatic cells). Thus, mutations that occur now may be responsible for diseases in future generations as well as in the present generation.

The Ames assay is used to determine whether a chemical is mutagenic for bacteria. A high proportion (85-90%) of the carcinogenic chemicals that have been tested in the Ames assay exhibit mutagenic activity. The Ames test gives false positives as well as false negatives, but the frequency of false positives is difficult to assess.

The CHO assay is also used to measure mutation. This assay is an important addition to the Ames assay since it allows the effect of chemicals to be measured in mammalian cells, which differ in important ways from bacterial cells.

The specific actions taken by Haskell and Industrial Departments on the basis of positive results from predictive assays will depend on a number of factors which include:

- availability of additional test data,
- cost of obtaining the additional data vs. expected benefits,
- extent and nature of the use or planned use for the specific chemical, and
- regulatory requirements for additional data.

In obtaining additional information the following are possible:

- Perform a predictive test on pure test material to assure that the mutagenic activity is not due to an impurity.
- Perform other short-term tests that measure mutagenic activity or the ability of a test material to damage DNA. The CHO assay that measures mutagenic activity in cultured mammalian cells is a logical choice to follow the Ames assay. In some cases it may be useful or necessary to perform assays that measure DNA damage and repair or damage to chromosomes.

- Perform subchronic studies to further define toxicity or chronic studies to evaluate carcinogenic potential.

- Determine if epidemiological information is available and whether it indicates that the test material has caused medical problems.

When the tested chemical is currently being used or a significant use is contemplated, and depending on information obtained above and the conditions of use, the Industrial Departments should give consideration to:

- Reviewing the potential for significant exposure and, if appropriate, institute additional control measures or procedures.

- Evaluating potential substitutes. Predictive assays are useful tools to help rapidly identify chemicals that have a low likelihood of being mutagens or carcinogens.

CFR/rlm

SHORT-TERM ASSAYS FOR IDENTIFYING POTENTIAL CARCINOGENS AND MUTAGENS

Procedure for follow-up of positive assay results

1. A representative of the Molecular Biology Section will notify the appropriate Haskell coordinator when the follow-up of a particular test result is to be initiated. The follow-up procedures will be initiated promptly.

2. The Haskell coordinator in cooperation with a Molecular Biology representative will contact the Haskell liaison and determine what the status or projected use of the test material is.

3. If the test material will no longer be used, made, or further developed, the Haskell liaison will notify the Haskell coordinator indicating this to be the case.

4. If the test material will be developed further or is being made or used, the Haskell coordinator will assemble and evaluate all of the available toxicity information except for the mutagenicity and short-term predictive oncogenicity data, which will be gathered and evaluated by members of the Molecular Biology Section.

5. The Haskell coordinator in cooperation with a Molecular Biology representative will arrange a meeting which will generally be attended by the coordinator, the Haskell liaison, an industrial hygienist, and a representative from the Molecular Biology section, and possibly others. The purpose of this meeting is to discuss the toxicity data, the composition and purity of the test material, the proposed usage, the exposure levels and potential for exposure, etc. A decision should be made on whether additional toxicity or other pertinent information is needed and whether additional measures to control exposure should be considered. In some cases a meeting may not be necessary to decide on an appropriate action.

In case of negative short-term assay results, a member of the Molecular Biology section in cooperation with the appropriate Haskell coordinator will contact the Haskell liaison from the department that submitted the chemical for testing. The status of development and the proposed or present use of the test material, as well as the potential for exposure will be determined. On the basis of this information, the possible need for more toxicity information will be discussed among the liaison, the coordinator, and a member of the Molecular Biology section.

DFK/CFR/rlm
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