PRESENT EPA PLANS RE TSCA TESTING REQUIREMENTS

U.S. PERSPECTIVE - N. Page

To evaluate the risk from chemicals requires two separate processes: (1) identification of potential hazards and (2) quantitation of those hazards in terms of total impact on man and the environment. The TSCA separates legal requirements for assessing chemical hazards into that for chemicals currently being manufactured (Section 4) and that for new chemicals (Section 5).

Basically, however, the data needs and manner with which they are utilized in risk assessment are the same. The ability to obtain certain data may be different. For example, epidemiologic evidence of human effects from prior exposure obviously can't be obtained for new chemicals. The same is true for residue levels in the environment or body tissues.

Thus, the data on which one estimates potential hazard will always be less than what one might desire. The U.S. is committed to "disaster prevention." We are committed to preventing the unleashing of toxic chemicals into the environment. The lessons we were taught by mercury, kepone, thalidomide, PCBs, but to name a few substances, should be long remembered. What is needed to assess the potential hazard of chemicals? We, of course, would like to have data on all possible harmful effects. We also need the insight in how to interpret such data in terms of risk to people and to the environment.

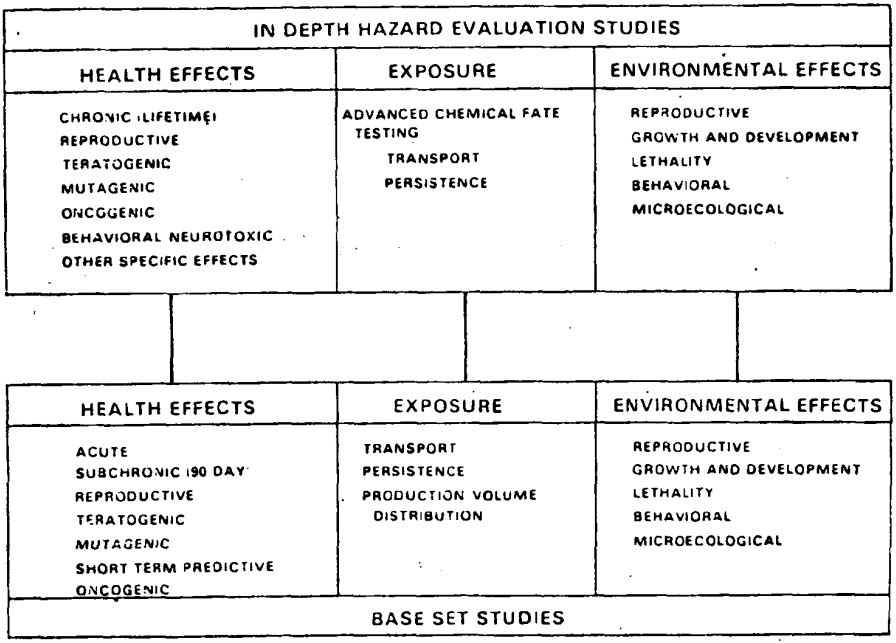
FROM: SOCMA
6/15/78

MONS 007956

Under Section 5, a manufacturer must provide the EPA with a 90-day advance notice of intent to manufacture a chemical. He must also submit data which will allow the agency to determine if the chemical will not present an unreasonable risk of injury to health or the environment. What data are needed to make such assessments? We recognize that we must reach a compromise between the amount of data that is needed to conduct a thorough and complete assessment and what is reasonable for new chemicals for which the market potential and thus the magnitude of exposure are not yet known.

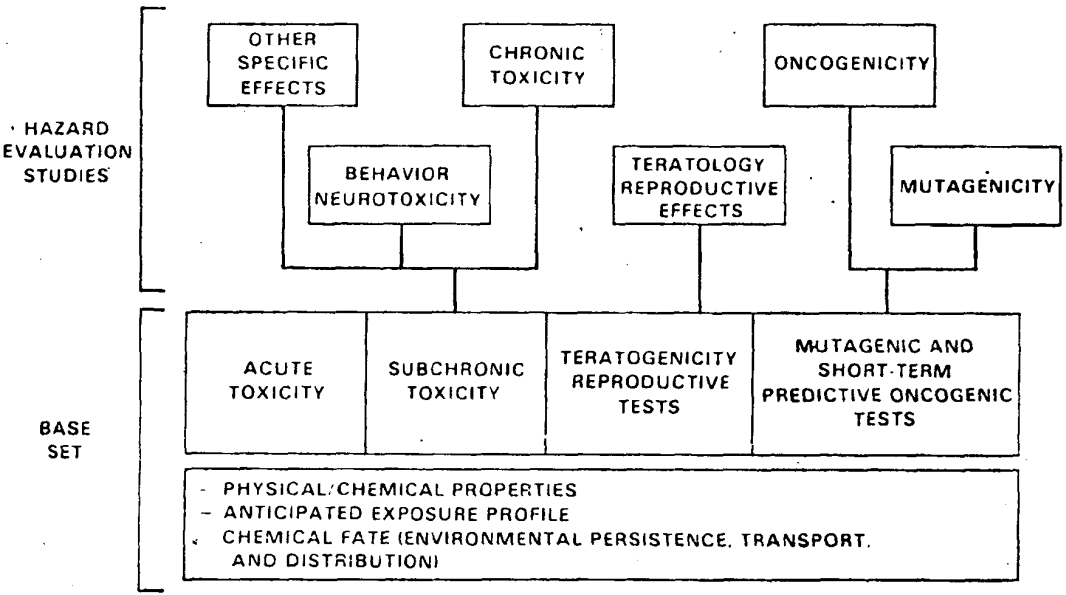
The concept that we are pursuing is that of a hierarchical or tier scheme for data generation. We have held many discussions with the scientific community on the best practical approach. The Conservation Foundation has been a big help in providing a forum for the presentation of viewpoints.

Where are we in our thinking? By fall the Agency is planning to have the proposed guidelines published in the Federal Register. We still have areas of recognized disagreement. There are soft areas which we need to firm up if indeed that is possible. We look forward today to a helpful discussion on these issues.


IN DEPTH HAZARD EVALUATION STUDIES
HEALTH EFFECTS
CHRONIC (LIFETIME)
REPRODUCTIVE
TERATOGENIC
MUTAGENIC
ONCOGENIC
BEHAVIORAL NEUROTOXIC
OTHER SPECIFIC EFFECTS
EXPOSURE
ADVANCED CHEMICAL FATE TESTING
TRANSPORT
PERSISTENCE
ENVIRONMENTAL EFFECTS
REPRODUCTIVE
GROWTH AND DEVELOPMENT
LETHALITY
BEHAVIORAL
MICROECOLOGICAL
HEALTH EFFECTS
ACUTE
SUBCHRONIC (90 DAY)
REPRODUCTIVE
TERATOGENIC
MUTAGENIC
SHORT TERM PREDICTIVE
ONCOGENIC
EXPOSURE
TRANSPORT
PERSISTENCE
PRODUCTION VOLUME
DISTRIBUTION
ENVIRONMENTAL EFFECTS
REPRODUCTIVE
GROWTH AND DEVELOPMENT
LETHALITY
BEHAVIORAL
MICROECOLOGICAL
BASE SET STUDIES

MONS 007958

TESTING SCHEME—HEALTH EFFECTS



MONS 007959

ACUTE TOXICITY TESTS

SINGLE DOSE LD_{50}

14 DAY OBSERVATION PERIOD

LIMITED PATHOLOGY

SPECIES (2) - RAT + NON-RODENT

BOTH SEXES

ROUTES (2) - ORAL AND OTHER (DERMAL OR INHALATION)

EYE IRRITATION TEST - RABBIT

DERMAL IRRITATION/SENSITIZATION TEST - RABBIT AND GUINEA PIG

MDNS 007900

SUBCHRONIC TOXICITY PROFILE

DURATION - 90 DAYS

SPECIES - RAT+NON-RODENT

BOTH SEXES

ROUTE - ANTICIPATED MAJOR HUMAN EXPOSURE

DOSES - 3
- HIGH DOSE - TOXIC RANGE
- LOW DOSE - NO-OBSERVABLE EFFECT

NO. ANIMALS - 20/SEX/DOSE

PATHOLOGY EXAMINATION - THROUGH GROSS EXAMINATION; MICROSCOPIC EXAMINATION OF ALL MAJOR TISSUES (ABOUT 30) (OPTION - LIVER, KIDNEY, TESTES, ALL LESIONS)

CLINICAL EXAMINATION -
- CLINICAL OBSERVATION - FREQUENT, CAREFUL (FOR ALL POSSIBLE TOXIC EFFECTS, INCLUDING BEHAVIOR, NEUROTOXICITY, OPTHALMIC, ETC.)
- HEMATOLOGY
- CLINICAL CHEMISTRY - ENZYMOLOGY
- TISSUE RESIDUES (FOR CHEMICALS THAT BIOACCUMULATE)

MONS 007961

SUBCHRONIC TOXICITY PROFILE TEST (OPTIONAL)

DOG – EXPOSURE FOR 90 DAYS

RAT – NUMBER – 4/SEX/DOSE (DOG)
20/SEX/DOSE (RAT)

– EXTENSIVE CLINICAL AND PATHOLOGY EXAMINATION

– 3 DOSE LEVELS AND CONTROLS
- HIGH DOSE - TOXIC RANGE
LOW DOSE - NO OBSERVABLE EFFECT

– ROUTE – EXPECTED HUMAN EXPOSURE

RAT – EXPOSURE: 90 DAYS COVERING SPERMATOGENESIS/BREEDING/EMBRYO-FETAL DEVELOPMENT/POSTNATAL DEVELOPMENT

PREMATING	MATING	GESTATION	POSTNATAL
4 WEEKS	3 WEEKS	3 WEEKS	3 WEEKS

– REMAINDER OF PROTOCOL AS ABOVE FOR RAT

MRNS 007962

TERATOGENICITY

ONE SPECIES (OPTIONAL 2)

NUMBER OF ANIMALS, 20 PREGNANT FEMALES (RAT, MOUSE)/DOSE

ROUTE MOST CLOSELY RESEMBLING THAT OF MAN

MINIMUM OF THREE DOSES + CONTROL

HIGHEST DOSE SHOULD INDUCE SOME SIGNIFICANT MATERNAL TOXICITY AS DEMONSTRATED BY BODY WEIGHT, REPRODUCTION OR OTHER TOXIC SIGN

NECROPSY

REPRODUCTIVE TOXICITY

ONE SPECIES (i.e., MICE)

ENOUGH FEMALES TO PRODUCE 10 LITTERS/DOSE

10 MALES

ROUTE MOST CLOSELY RESEMBLING THAT OF MAN

MAXIMUM OF 3 DOSES (GIVEN DAILY) + CONTROL

MONS 007963

SHORT TERM MUTAGENICITY AND ONCOGENICITY TEST BATTERIES

I. TO DEFINE A NONMUTAGEN

- 3 GENE MUTATION TESTS
- 1 CHROMOSOME ABERRATION TEST
- 2 DNA DAMAGE TESTS

II. TO SET PRIORITIES FOR MAMMALIAN ONCOGENICITY TESTING

- 3 GENE MUTATION TESTS
- 1 CHROMOSOME ABERRATION TEST
- 2 DNA DAMAGE TESTS
- 1 IN VITRO TRANSFORMATION TEST (OPTIONAL)
- OTHER TESTS MAY BE ADDED AS THEY ARE DEVELOPED

MONS 007694

ONCOGENICITY TEST STANDARDS

- 2-YEAR STUDY
- 2 RODENT SPECIES/BOTH SEXES
- SIMULATES ROUTE OF HUMAN EXPOSURE
- 5 DOSE LEVEL MINIMUM
  - 4 CHEMICAL LEVELS PLUS MATCHED CONTROL(S)
  - RANGE SPACED TO INCLUDE .01 HDL AND HDL
- CLINICAL AND MORTALITY OBSERVATIONS
- CLINICAL CHEMISTRY AND HEMATOLOGY
- HISTOPATHOLOGIC EXAMINATION
- FORMAT OF RESULTS
  - SUMMARY TABLE
  - CONTENTS OF SUPPORT DATA
- PROTOCOL SUBMISSION TO EPA 90 DAYS BEFORE INITIATION OF STUDY
- CONDUCT OF STUDY UNDER QUALITY ASSURANCE STANDARDS

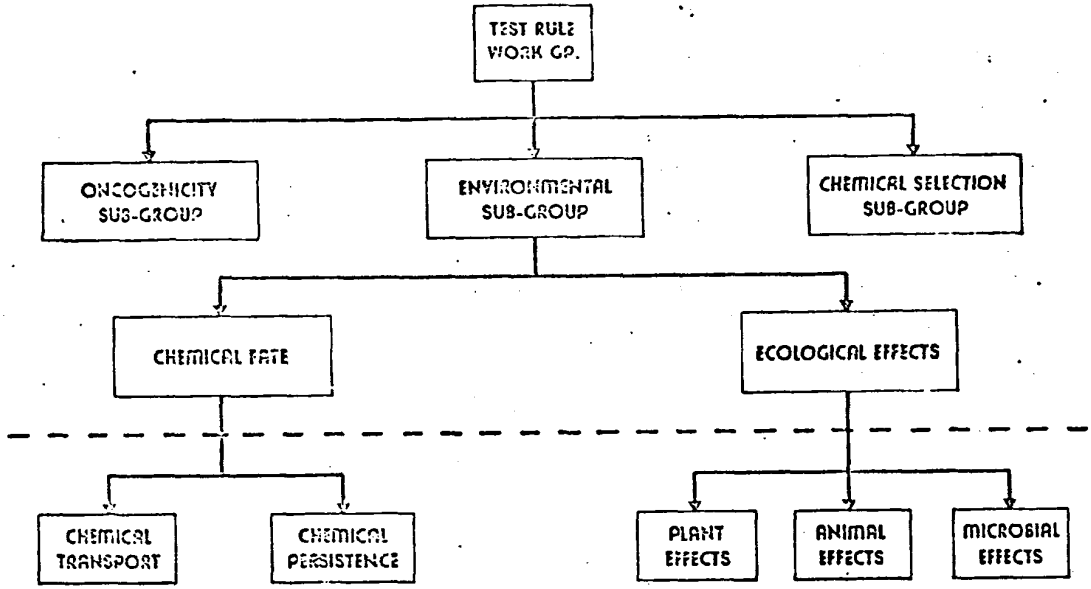
MONS 007965

CHRONIC TOXICITY TEST STANDARDS

- LIFE TIME STUDY
- TEST SPECIES/BOTH SEXES
  - RAT
  - DOG (OR OTHER NON-RODENT WITH EPA APPROVAL)
- SIMULATES ROUTE OF HUMAN EXPOSURE
- 5 DOSE LEVEL MINIMUM
  - 4 CHEMICAL LEVELS PLUS MATCHED CONTROL(S)
  - RANGE SPACED TO INCLUDE NO EFFECT LEVEL AND HDL
- CLINICAL AND MORTALITY OBSERVATIONS
- CLINICAL CHEMISTRY AND HEMATOLOGY
- FUNCTION TESTS
- HISTOPATHOLOGIC EXAMINATION
- FORMAT OF RESULTS
  - SUMMARY TABLE
  - CONTENTS OF SUPPORT DATA
- PROTOCOL SUBMISSION TO EPA 90 DAYS BEFORE INITIATION OF STUDY
- CONDUCT OF STUDY UNDER QUALITY ASSURANCE STANDARDS

MONS 007966

TEST RULE WORK BREAKDOWN STRUCTURE



MONS 007967

SELECTED PARAMETERS FOR PREDICTING CHEMICAL TRANSPORT

- SOLUBILITY
- VOLATILITY
- ADSORPTION
- DESORPTION
- PARTITION COEFFICIENT

MONS 007968

PROBLEMS TO BE ADDRESSED IN DEVELOPING TEST PROTOCOLS FOR CHEMICAL TRANSPORT

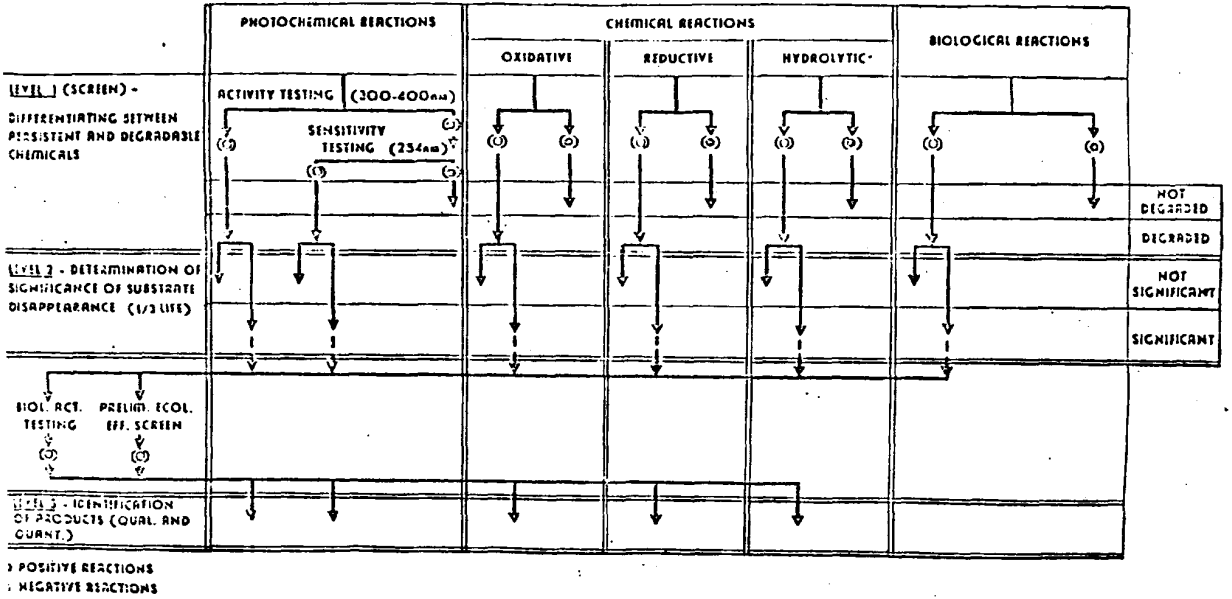
MONS 007969

- IDENTIFYING AND INCORPORATING ENVIRONMENTAL VARIABLES INTO TEST REQUIREMENTS

- EXTRAPOLATING LABORATORY RESULTS TO PREDICTIVE ENVIRONMENTAL BEHAVIOR

- USE OF REFERENCE MATERIALS

PERSISTENCE TESTING



MONS 007970

ECOLOGICAL EFFECTS TESTING

MONS 007971

LIFE FORMS TO CONSIDER

- **ANIMALS**
  - VERTEBRATES
  - INVERTEBRATES
- **PLANTS**
  - HIGHER
  - LOWER
- **MICROORGANISMS**
  - AEROBES/ANAEROBES
  - HETEROTROPHS/AUTOTROPHS
  - PHOTOSYNTHETIC/CHEMOSYNTHETIC

ECOLOGICAL EFFECTS TESTING

ECOSYSTEMS OF CONCERN

- AQUATIC
  - FRESH
    - WARM
    - COLD
  - SALINE
    - OCEANIC
    - ESTUARINE
- TERRESTRIAL
  - SOILS
    - CULTIVATED
    - UNCULTIVATED
  - SEDIMENTS
    - FRESH WATER
    - SALINE WATER
- ATMOSPHERIC

MONS 007974

COST ESTIMATES (HEALTH EFFECTS TESTS)

— BASE SET —

ACUTE STUDIES		
ORAL ADMINISTRATION	RAT	$ 850
	DOG	900
DERMAL ADMINISTRATION	RABBIT	600
INHALATION ADMINISTRATION	RATS	1,500
EYE IRRITATION	RABBITS	400
DERMAL IRRITATION	RABBITS	400
DERMAL SENSITIZATION	GUINEA PIGS	400
SUBCHRONIC	RATS	15,000
MUTAGENIC TEST/ONCOGENIC INDICATIVE TEST	—	15,000
TERATOGENIC TEST	(i.e., MICE)	8,000
REPRODUCTIVE TEST	(i.e., MICE)	8,000

1/

MONS 007973