File: MCA -
Topic Substances
Control Group

January 21, 1977

J. R. McDonough, M.D.
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Dear Dr. McDonough,

Dan Palm has passed on to me a copy of your draft on "Developing Approaches to Toxicology Testing." Unfortunately, I did not receive the draft until January 19 and so obviously could not have comments to you by January 17. Others appeared to have made some detailed comments, so I will make only a couple of comments and suggestions.

In the introduction, you state, "We must at all costs avoid the grim saga of PCBs, vinyl chloride, and asbestos." Then, in the next line you go on to say that it is not certain that we can avoid such occurrences in the future. I doubt if we are willing to accept the cost of not doing any further development of new chemicals in order to avoid another grim saga. We are willing to accept some level of risk in order to obtain the benefits that we may be able to derive from a new material. I believe it would be harmful to the chemical industry to have one of our representatives quoted as saying that we must at all costs avoid such incidents.

In the next to the last paragraph on page 7, you give the cost of a carcinogenicity study as being in the range of $100,000. Inhalation carcinogenicity studies involving two species are presently costing $300,000 to $400,000. I believe that the $100,000 figure may be too low and misleading.

Relative to George Ingle's comment on cost effectiveness, there is some logic inputting the Ames type of testing, the dominant lethal tests, and the teratogenicity testing before the lifetime carcinogenicity tests. I believe that if we had strong positives in all three of these tests, we could take a hard look at the probable profitability before committing $300,000 for an inhalation carcinogenicity test.

OLI 3611

There might be some mention made of fish and wildlife tests since TOSCA does specify effects on the environment as well as effects on health of humans.

I appreciate the privilege of being able to read the draft of your presentation and hope that the above comments may be of some value to you. You have undertaken an extremely difficult task and have developed a fine summary of the state of the art.

Very truly yours,

RH

Richard Henderson, Ph.D.
Director, Health Sciences
and Toxicologic Research

RH:pan

cc: D. B. Palm

TOXICOLOGICAL TESTING

Slide 1

Tests currently available

Reliability

Information derived from test

Limitations

Approach under the law

Slide 2

Acute Study (Range finding)

Prolonged (Subchronic)

Chronic

Slide 3

Carcinogenicity

Mutagenicity

Teratogenicity

OLI 3613

Sample Acute Test

Slide 4

Male Rats (150-200g)
- 5 at low dose
- 5 at intermediate dose
- 5 at high dose

Material by mouth

Observed 7-14 days

Standard diet

LD_{50} calculation

de 5

Test	Cost	Time
Acute oral LD_{50} - 2 species	$1,000-1,200	6 weeks

Toxicity Ratings Based on Acute LD_{50}

Slide 6

Relatively nontoxic	5g to 50g/kg
Slightly toxic	500mg to 5g/kg
Moderately toxic	50mg to 500mg/kg
Highly toxic	1mg to 50mg/kg
Extremely toxic	less than 1mg/kg

[illegible] many [illegible] of the acute — observation some slightly toxic substances on acute basis are carcinogenic or teratogenic.

OLI 3614

Prolonged Test

Slide 7

Rats (or dogs)
10-20 control
10-20 low dose
10-20 intermediate dose
10-20 high dose

Administration - By mouth, inhalation, injection, skin

Duration 30 to 90 days

Prolonged Test (continued)

Slide 8

Periodic evaluation of animals

- Body weight
- Physical Exam
- Blood chemistries
- Urinalysis
- Hematology

Observation of Animals

- Activity
- Behavior
- General appearance

Animals subject to autopsy and histology

Slide 9

Test	Cost	Time
Prolonged (Subchronic) Studies		
90 day rat feeding	$12-14,000	6 months
90 day dog feeding	$17-20000	

Slide 10

Carcinogenicity Test

Rats or mice 200 animals 50 in each of 4 dosage groups
100 animals in control group

Total 300 animals

Route of Admin. - oral, inhalation, skin, other

Duration - 2 to 3 years

Observations - blood chemistries, hematology, pharmacokinetic studies, weight changes, general demeanor.

Slide 11

Test	Cost	Time
Chronic Feeding Study (Comer)		
Rat 2 yr.	$70-90,000	30 months
Dog 2 yr.	$80-100,000	30 months

OLI 3616

Slide 12 — Mutogenicity Tests

Cytogenetic Analysis

Mutation in microorganisms

Host-mediated assay

Dominant Lethal

DNA repair studies

Slide 13

Mutogenicity Studies	Cost	Time
Host-mediated assay	$2-2500	2-3 months
Dominant Lethal	$8-9000	4 months
Cytogenetic Studies	$7-8500	4 months

Slide 14

Food

Housing

Climate

Biological factors

OLI 3617

Slide 15

80 Female rats

- 20 control
- 20 low dose
- 20 intermediate dose
- 20 high dose

Dosage - daily during day 6-15 of pregnancy.

Observations

Slide 16

Autopsy - 1. Spontaneous deaths and moribund animals.

2. Survivors on day 30 of pregnancy

3. Examinations

4. Term fetuses - weighed, measured and examined

Slide 17

Test	Cost	Time
Rat	$7-15,000	4 mos.
Mouse	$6-9,000	4 mos.
Monkey	$50-65,000	14-16 mos.