FROM (NAME & LOCATION): G. Wentwo.ch

DATE: November 26, 1974

SUBJECT: New Safety Measures for Handling Halogen-Containing Monomers

REFERENCE:

TO: Distribution

Distribution:
Y. G. Bryant
R. A. Evans
E. W. Folk
R. G. Garmon
P. H. Hobson
J. R. Kirby
R. S. Knorr
J. C. Masson
G. Palethorpe
S. A. Roberts
R. B. Thompson

Because of the probable toxicity of monomers such as VCl_2 and VBr, it is imperative that personnel exposure to these monomers be kept to an absolute minimum. With the active assistance of all of the polymer technicians, Roger Evans and I are attempting to make immediate changes in our methods of operation. To determine whether these changes are effective, we must monitor air-borne halogen levels during every polymer preparation (Pfaudler, CP, PCP) for the next several weeks. In order to arrange for this monitoring, I must now ask that anyone planning to make a polymer containing VBr or VCl_2 give me at least 24 hours' notice, describing the monomer levels and apparatus to be used.

In general, the new procedures will mean that more time must be alloted to make a polymer run. In addition, a substantial amount of technician time will be required to modify existing apparatus and procedures. The changes being made will require large doses of patience and cooperation from each of us, but they should ensure both our continued health and our continued operation.

For the present we'll operate on verbal instructions for changes in procedure. This will be followed by written OI's within two or three weeks.

Gary

G. Wentworth

AG4/74-109/oo

[redacted]

[redacted]

TOXICOLOGY

TOXICOLOGY

Goals

The goal of the toxicology section is to obtain a complete description of the spectrum of biologic effects of materials important to Monsanto. The section will seek to achieve this goal by expanding the quality and quantity of toxicity data on materials of interest to Monsanto. Quality pertains to more than excellence of toxicity data. It relates to the nature of the process by which those data are developed, encompassing variety of tests and depth of testing. Quantity refers solely to the number of products or intermediates judged to have been tested to an acceptable level.

Over the years, animal tests which had been used in special circumstances have been incorporated into routine safety evaluations. Thus, words such as carcinogenicity, mutagenicity and teratogenicity have come into everyday use. Since tests for these effects are time-consuming and expensive, attempts are being made to develop short-term screening tests, such as microbial mutagenicity which can be used as an indicator of carcinogenicity to provide rapid estimates of potential long-term hazards. Finally, concern over environmental effects of chemicals has led to studies of their effects on fish and wildlife and to the determination of biodegradability and bioaccumulation of materials. These three factors have contributed to the increased variety of procedures included in the quality of toxicity testing.

The depth of toxicity testing depends on the nature of the material and its intended uses. It would include determination of (1) the effect(s) produced in animals, (2) the amounts required to produce the effect(s) and, (3) the amounts which can be tolerated without observable effects. While close, intensive scrutiny will increase the probability of detecting adverse effects, it is neither necessary nor possible to give every material the same detailed examination. Consequently, it is necessary to make judgements in the selection of materials for study and the tests which are to be conducted on them.

We estimate that approximately 10% of the products and intermediates which Monsanto handles have been tested to an acceptable level. Initiation of needed in-depth toxicity tests on a half-dozen, or even a score, of materials would reduce the backlog of a few thousand substances by only a fraction of a percent per year. Thus, it will be necessary to increase contacts with other researchers throughout the world to determine which materials they have studied, are investigating, and plan to test. Using that information to guide our programs, we can provide greater assurance that adequate toxicity data will be available on compounds of major interest to Monsanto. Ultimately, it must be recognized that priorities and judgements will dictate which chemicals are studied and the depth of this testing.

Functions

The FUNCTIONS of the toxicology section are to use toxicity data to help Monsanto:

1. Keep products on the market for uses judged to be safe,
2. Market new and existing products,
3. Stop development of products judged to present unusual health or environmental hazards,
4. Restrict sales, if necessary, of selected products to specified uses, and
5. Guide its research projects.

Toxicity data is used to ACHIEVE these functions by:

1. Estimating "safe" and "unsafe" uses and handling conditions,
2. Providing Industrial Hygiene with a basis for establishing permissible personnel exposure levels,
3. Providing Physicians with diagnostic clues for monitoring exposed individuals, and
4. Providing Process Environment with guidance on environmental effects of chemicals.

This will be ACCOMPLISHED by:

1. Searching the literature for,
2. Developing,
3. Evaluating, and,
4. Disseminating toxicity data as it pertains to health and environmental hazards of chemicals.

RESOURCES available for these purposes include:

1. Monsanto's Environmental Health Laboratory, (Mid 1978)
2. Professional staff in DMEH,
3. Professional staff elsewhere in Monsanto,
4. Consulting laboratories,
5. "ad hoc" task forces (acrylonitrile, butadiene, chlorobenzenes, epichlorohydrin, vinyl bromide, vinyl chloride, vinylidene chloride are current examples),

6. CIIT,

7. Trade associations,

8. Government agencies (National Cancer Institute, National Institute for Environmental Health Sciences, Environmental Protection Agency, Food and Drug Administration, etc.)

9. International agencies (International Agency for Research on Cancer, a unit of the World Health Organization), and

10. Professional societies.

Predictions

In developing a plan to meet these goals and fulfill our function, certain events that will affect the operations are postulated. These include:

1. The amount and variety of toxicity data needed to maintain existing products or to market new products will increase.

   A. Toxic substances legislation and/or regulatory requirements of other agencies will increasingly dictate what is to be done. As resources are spent on what is dictated to us, toxicity testing will have to expand if we are also to do studies we believe are needed to protect Monsanto's interests.

   B. Allegations of adverse human or environmental effects will lead to incorporation of additional toxicity tests, aimed at answering specific questions, into safety evaluations.

   C. Worldwide concern over health hazards of chemicals will increase. This will be reflected in special test requirements which specific countries will adopt.

2. Emphasis will shift to subtle, chronic effects of chemicals such as behavioral changes and alterations in physiological parameters without clinical signs of impairment.

3. Teratologic, reproductive, and mutagenic effects of chemicals will command more attention as increased numbers of women enter the chemical workforce, and as chemicals are identified in the general environment.

4. Studies on the biological transformation of foreign compounds will become more important. These will be needed to understand how chemicals behave in man and in the environment.

5. Concern over the effects of pesticides on wildlife and nontarget organisms will spread to encompass unintended adverse effects to the environment from all chemicals.

6. The search for short-term tests as screening procedures to evaluate potential harmful effects of chemicals will intensify. Premature publicity given to the findings of these tests before their significance has been evaluated will pose threats to many materials.

7. Epidemiological studies in man and ecological surveys of the environment will be required to justify continued use of some materials.

8. The Environmental Health Laboratory and its Aquatic Toxicity satellite will be operating and the former will have been enlarged at least once.

9. Laboratory accreditation will be a reality and there may be some form of individual certification.

10. Government agencies will routinely audit laboratory practices and raw data from all chronic studies.

11. It is probable that less hazardous products will replace current ones without regard to considerations of economics or efficacy.

12. The increasing amount of toxicity testing and government activity will make it more difficult to keep abreast of regulations, literature, and programs of government agencies, trade associations, regional groupings, and special "ad hoc" committees.

13. Although successes may go unnoticed, failures will be highlighted. While all events cannot be foreseen, attacks on more prominent, profitable products can be minimized.

Program

Since all studies cannot be done on all products simultaneously, priorities for study must be established. Thus, an integral part of the program requires decisions to be made in the selection of materials and the tests to be performed on them. Priorities can be assigned on the basis of commercial importance, concerns of customers, business or public groups regarding inherent or alleged toxicity, and the availability of toxicity data. An advisory committee, consisting of representatives from the operating companies and DMEH can develop these priorities.

Literature Surveillance

Prior to development of new research data on any chemical, a thorough evaluation of existing information is made to determine its extent and current validity. This includes:

1. A survey of in-house data (Appendix 1, Page 47, Shows a sample)

2. Assimilation of other Monsanto data (biodegradation, fish toxicity, tissue residues, etc.) into DMEH files

3. A review of published literature covering experimental and clinical experience with the product and related chemicals. (Appendix 2 Page 48 Library of Medicine Toxline Computer Printout)
4. Contacting other agencies conducting toxicity testing to determine if they have unpublished data or if they are studying compounds of interest to us. (Appendix 3, Page 53)
5. Development of a procedure for continuous surveillance of literature to keep knowledge current and up-to-date.

Toxicity Testing

1. Acute toxicity and irritation data will be developed on all Monsanto products. This is the minimum information needed for precautionary labeling and freight classification and it provides a basis for preparing Toxicity and Handling Statements. (Appendix 4, Page 59)
2. Acute toxicity and irritation data will be developed on all intermediates and by-products handled in Monsanto if such information is not otherwise available.
3. Status of toxicity data on all agricultural products will be reviewed to determine whether it is adequate to meet current standards. This will require additional testing on older products if they are to continue to be marketed.
4. There is very little toxicity data on most rubber chemicals. Testing programs will be developed to define working conditions under which they can be made and used safely.
5. Toxicity data needed for commercialization of new materials will be developed during the incubation period between concept and commercialization of a new product.
6. As new uses of existing products arise, available toxicity data will be reviewed to determine its adequacy for the new use and for continuation of existing uses. If needed, additional testing will be initiated.
7. New products which are variations of existing products will trigger a review of the toxicity data on the related products. A testing program will be developed to cover needed toxicity tests on the new product and obvious gaps in our knowledge on the related products.
8. Annually, broad screening studies will be started on six selected existing products in addition to the on-going programs on new products. Insofar as possible, these screening tests will be standardized in order to obtain data that will allow comparisons of results obtained on different materials at different times and in various laboratories. These studies are designed to identify target organs or other specific effects and to establish no-effect levels. A selected series

of test protocols is shown in Appendix 5, Page 60.

These screening tests can identify specific adverse effects. Further testing may show them to be dose-related or may provide a rational basis for defining safe conditions of use. Portions of these protocols are directed toward worker exposure which requires information on effects of inhalation, contact hazards, and systemic effects. Others are more directly related to consumer exposure which requires information on acute and chronic effects and demonstration of a no-effect exposure level.

Restriction to six products is based on availability of in-house staff to formulate protocols, monitor studies, and evaluate results, and prepare information for dissemination through data sheets, white papers, scientific publications, internal guidelines, and other means.

In addition, there are limited numbers of commercial laboratories with acceptable capabilities. The number of products to be studied will be increased by development of the Environmental Health Laboratory (EHL) (which will approach maximum productivity about 1980), by establishing working relationships with more laboratories and aiding them to upgrade their quality control and reputation, by initiating cooperative studies on common products or intermediates with other companies, and by participation in the Chemical Industry Institute of Toxicology (CIIT).

Our current long-term toxicity testing program (Appen. 6, Pg. 63) has resulted from the preceding activities. The table shows the year in which testing of a material was started. Since most of these products are undergoing multiple tests, and since some of the tests span 2-3 years, the annual addition of new materials will lead to an expanding overall workload. The actual level at which this will plateau will be determined by available resources of laboratory space and, more importantly, qualified scientists to conduct the tests and evaluate the significance of the findings.

Coordination of Programs

The EHL will become the focal point around which our toxicology program will revolve. As it becomes functional, it will undertake portions of the testing program now being conducted at consulting laboratories. While the laboratory will be capable of conducting a wise range of studies, it will enable a greater emphasis on inhalation toxicity, metabolism studies, and in vitro procedures. In addition, the staff of the laboratory will increase the depth and breadth of our expertise in the various areas of toxicology.

The increasing emphasis on employee exposure and air pollution in general has led to a serious shortage of inhalation facilities. The new laboratory will enable us to provide for a large measure of Monsanto's needs in this area.

Metabolism studies will be needed to answer questions about biochemical transformations which chemicals undergo in man and the environment. Knowledge of these transformations is needed to understand how chemicals behave in the biosphere and why they do or do not produce effects in the environment.

Non-mammalian test systems, microbes and tissue cultures, are being employed with greater frequency. Extrapolations of findings from such studies are used to indict chemicals. It will be necessary to evaluate the technical implications of using non-mammalian systems and to assess their relevance in estimating potential health or environmental threats. The new laboratory will provide space for expansion of the limited program started this year in "N" building to perform and to weigh the significance of such tests.

An expanded aquatic toxicity testing facility is needed to centralize research in this area and to provide for better integration of environmental and mammalian test programs. A separate acquatic laboratory possibly at St. Peters has been proposed as a satellite of DMEH (Appendix 7). At present, Monsanto's aquatic toxicity testing is concentrated primarily in "N" building. Those facilities are overtaxed by demands of the Detergents and Phosphates Division alone. This requires other business groups to do virtually all of their testing at outside laboratories.

Staff toxicologists, separate from those assigned to the laboratory, also will be needed to coordinate activities. These will involve contacts with consulting laboratories, liaison with other groups conducting toxicity testing, interfacing with regulatory agencies, and editing available data into forms suitable for use, including publication.

Dissemination of Data

Every criticism or allegation of harm cannot be anticipated. Questions can be raised before satisfactory answers have been developed on a material, and questions may arise regarding materials believed to have been studied adequately. This will require diversion of time and talents to investigate those questions. In addition, any testing program can give ambiguous or spurious results requiring further testing. Nevertheless, the following approaches will be undertaken.

1. Toxicity and Handling Statements (Appendix 4) will be prepared on all products. Toxicity data will need to be developed on some products, and previously prepared statements may need revision. At the rate of

40-50 per month, it will take approximately 10 years to prepare statements for the estimated 4,000 - 6,000 products Monsanto has.

2. Available toxicity data will be used to prepare internal guidelines for employee exposures. When data are deemed adequate, they will be collected, evaluated and forwarded to the American Conference of Governmental Industrial Hygienists with a request that they establish a Threshold Limit Value (TLV) for the material. TLVs established by that group can influence legal exposure limits for workplace atmospheres adopted by the Occupational Safety and Health Administration. (Appendix 8, Page 65).

3. A summary of Monsanto and literature information will be prepared on each product and intermediate for ready reference. This will include environmental and toxicity data.

4. As toxicity data is developed on important products, detailed white papers will be prepared. These will contain a summary of toxicity data and will include judgements as to the overall risks associated with use of materials.

5. Publication of toxicity and environmental data in the open literature will be accelerated. This will give public and professional recognition to the scientific staff and Monsanto, will provide peer review of our data, and may forestall unwarranted criticism of products.

6. If products are judged to present unusual health or environmental hazards, the appropriate Monsanto unit will be alerted as soon as possible and, if necessary, appropriate regulatory agencies. If the risks are judged to outweigh benefits, the product can be eliminated at an early stage of development. Alternatively, it may be necessary to restrict sales to specified uses; i.e., those in which the benefits are judged to outweigh the risks. The indicated restriction on sales may lead to elimination of the product.

7. Toxicity data, particularly the results of short-term testing, can be used to guide selection of prospective products from a series of potential candidates. Alternatively, accumulated toxicity data can be employed to choose compounds which will have a greater probability of safety for specific uses.

Needed Resources

The proposed manning table for the EHL and the sequence in which it is to be staffed are shown in Appendix-9) . . As the laboratory becomes operational, additional technicians and/or animal caretakers may be needed to fully exploit its potential.

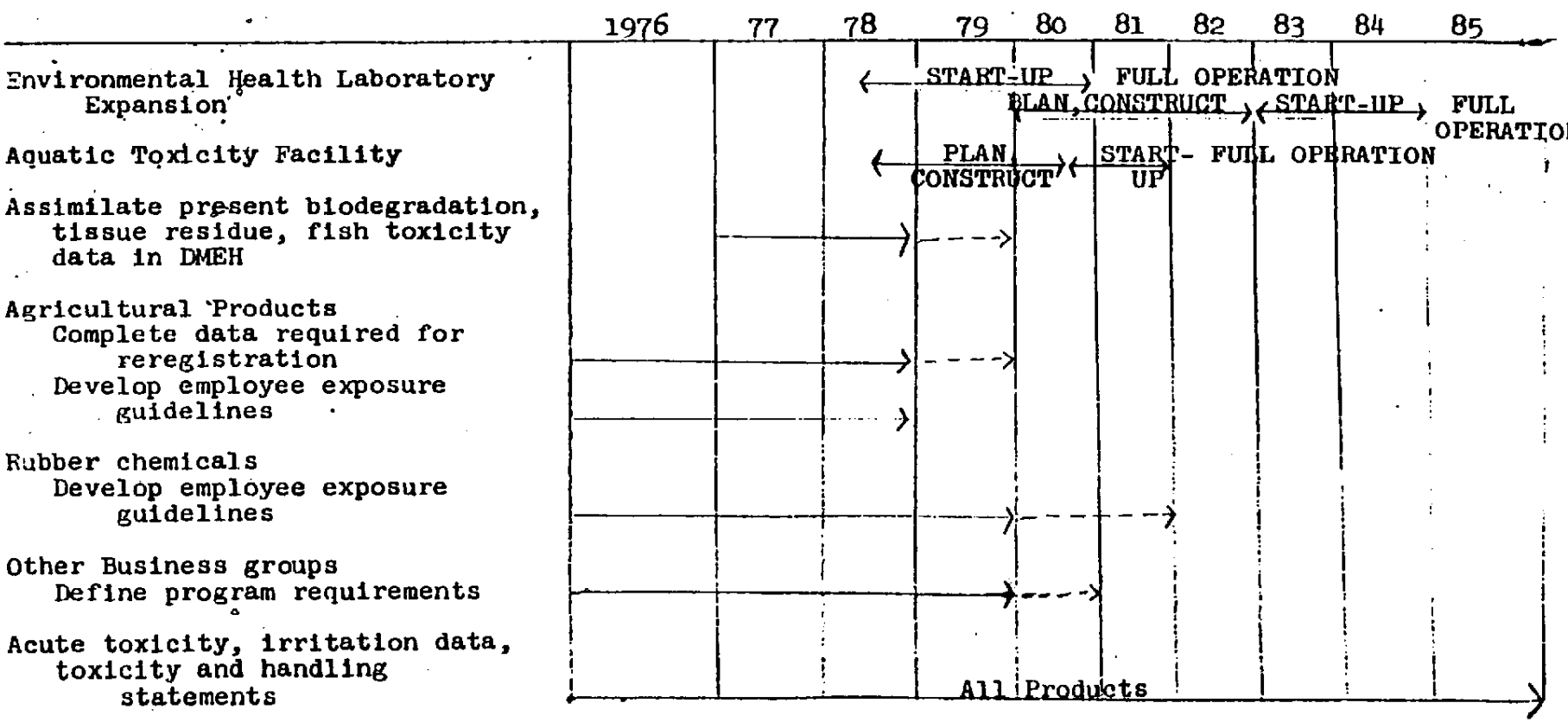
By 1980, the section will have undergone a major expansion and the EHL will be in full operation. That will be an opportune time to review current programs and to plan expansion of the laboratory. The expansion can be directed toward those areas of toxicology in which facilities are limited or which are deemed critical to Monsanto's interest. The planned expansion will cost $10 to $12,000,000. It will increase laboratory and animal holding space by 80%, and require an additional staff of about 50 people. (Appendix 10) The distribution between scientists, technicians, and animal caretakers will be determined by the nature of the planned programs. If the emphasis is on metabolic and special studies, a greater proportion of scientists will be added. If the shift is to carcinogenic and reprcductive studies requiring large numbers of animals, technicians and animal caretakers will be needed.

A separate aquatic facility will cost approximately $1,000,000. This preliminary estimate will be refined when definitive design begins. About 12 persons will be required to staff the installation. (Appendix 11) The exact number will be influenced by the scope of the operation and the availability of round-the-clock security. It is anticipated that funds for this laboratory will be sought in 1978.

An estimated six additional staff toxicologists will be needed for functions described earlier. These additions should come within the next three years.

It may appear illogical to request permission to hire additional toxicologists when we are unable to fill existing vacancies. However, we need authorized positions against which to recruit, and we could effectively use additional toxicologists at present. Monsanto's decision to build a toxicity laboratory has aroused interest in several areas. This should improve our ability to attract qualified people. During the next few years, we will be able to offer opportunities to both laboratory and non-laboratory scientists.

TOXICOLOGY PLANS



TOXICOLOGY RESOURCES

ersonnel	1976	77	78	79	80	81	82	83	84	85
ection Manager	1	1	1	1	1	1	1	1	1	1
taff Toxicologist	4	6	8	10	10	10	10	10	10	10
lerical	1.5	1.5	1.5	2	2	2	2	2	2	2
nvironmental Health Laboratory										
Manager		1	1	1	1	1	1	1	1	1
Scientist (PhD)		4	10	11	11	11	11	15	20	20
Scientist (BS/MS)	1	4	9	11	11	11	11	17	22	22
Clerical		1	2	3	3	3	3	4	5	5
Technician		1	10	15	15	15	15	23	30	30
Animal Caretaker			4	7	7	7	7	13	18	18
Equipment Cleaner			2	2	2	2	2	4	4	4
quatic Toxicity Laboratory										
Manager				1	1	1	1	1	1	1
Scientist (PhD)					2	2	2	2	2	2
Scientist (BS/MS)						1	1	1	1	1
Clerical						1	1	1	1	1
Technician					1	5	5	5	5	5
Fish Caretaker					1	2	2	2	2	2
Consultants	←			A s	N e e d	e d				→
Totals	7.5	19.5	48.5	64	68	75	75	102	125	125
Capital ($1,000			1,000	20	12,000	20	20	30	35	35

Appendix 1

(Printout from Microfiche reader)

[redacted] 0 3 [redacted]

ITEM NUMBER 3019 CAS NO. CP 041962

SYNONYMS:
AZO-BIS-ISOBUTRONITRILE
ABN CATALYST
VAZO 64-DUPONT
AIBN CATALYST

CHEMICAL NAME: CP 041962
ALPHA,ALPHA PRIME AZODIISOBUTYRONITRILE

WLN :
NCX&&MUNXCN

EMPIRICAL FORMULA:
C8-H12-N4

* Y-73-0278 * ORAL LD-50 M + F RATS (MG/KG)	* Y-73-0278 * DERMAL LD-50 M+F RABBIT (MG/KG)	* Y-73-0278 * EYE IRRIT M+F RABBIT AVE. MAX (MAXIMUM)	* Y-73-0278 * SKIN IRRIT M+F RABBIT AVE. MAX. (MAXIMUM)
200	>5010	0.6 NON-IRRITATING	0.0 NON-IRRITATING

ABT-73-0054 * INTERPRETATION
90-DAY SUBACUTE ORAL TOXICITY IN DOGS
LEVELS TESTED: 50,150,300 AND 1000 PPM
NO EFFECT LEVEL: 50 PPM
MICROSCOPIC LIVER CHANGES AT 150 PPM AND ABOVE

ABT-73-0057 * INTERPRETATION
001 90 DAY SUBACUTE ORAL TOXICITY IN RATS
LEVELS TESTED: 0,50,150 AND 300 PPM
NO EFFECT LEVEL: 300 PPM

[redacted] 1 3 [redacted]

CP 041962

Appendix 2
(page 1 of 5)

SI - PESTAB/76/1033
AU - Gallo MA ; Bachmann E ; Golberg L
1 TI - Mitochondrial effects of 2,6-dichloro-4-nitroaniline and its metabolites.
SO - Toxicol. Appl. Pharmacol. 35(1): 51-61; 1976. (18 references)
JC - TXAPA
AB - PESTAB. The effects of 2,6-dichloro-4- nitroaniline (DCNA) and its primary mammalian metabolites 3,5-dichloro-4- aminophenol (DCAP) and 2,6-dichloro-p- phenylenediamine (DCPD) were studied on isolated rat liver mitochondria in vitro and ex vivo. DCNA and DCAP inhibited electron transport and uncoupled oxidative phosphorylation in vitro at 10 mum while DCPD produced only slight uncoupling at 0.2 mM. Ex vivo studies at 1000 mg/kg p.o. or 500 mg/kg p.o. revealed a slight increase in respiratory rate and an increased sedimentation coefficient of isolated mitochondria. Urine analysis indicated two pathways of DCNA metabolism in the rat, but interconversion of DCPD to DCAP could not be demonstrated. (Author abstract by permission)

SI - CA/082/149997F
AU - Vasilenko NM ; Zvezdai VI ; Kovalenko II
2 TI - Inactivation of the blood respiratory pigment under the effect of aromatic nitro and amino compounds from the benzene series
SO - Sovrem. Probl. Biokhim. Dykhaniya Klin., Mater. Vses. Konf., 2nd: VOL 1,, 1972, P411-13
LA - Russ
JC - 29LJA
AB - CBAC COPYRIGHT: CHEM ABS when administered orally to rats at 0.1-0.2 LD50 for 30 days, aniline, m-chloroaniline (I), nitrobenzene, o-nitroaniline, p-nitroaniline, o-chloro-p-nitroaniline, p-chloro-o-nitroaniline, p-nitrochlorobenzene, m-nitrotoluene, dinitrotoluene, or trinitrotoluene (II) caused transformation of Hb into methemoglobin, nitrosylhemoglobin, and sulfhemoglobin. An increase in the levels of methemoglobins and sulfhemoglobins was accompanied by a decrease in oxyhemoglobin, but the total level of Hb remained unchanged. (62-53-3 Aniline) (108-42-9 m-Chloroaniline) (98-95-3 Nitrobenzene) (88-74-4 o-Nitroaniline) (100-01-6 p-Nitroaniline) (121-87-9 o-Chloro-p-nitroaniline) (89-63-4 p-Chloro-o-nitroaniline) (100-00-5 p-Nitrochorobenzene) (99-08-1 m-Nitrotoluene) (25321-14-6 Dinitrotoluene) (118-96-7 Trinitrotoluene)
RN - 62-53-3, 108-42-9, 98-95-3, 88-74-4, 100-01-6, 121-87-9, 89-63-4, 100-00-5, 99-08-1, 25321-14-6, 118-96-7

SI - CA/082/047716W
AU - Catronovo FP Jr ; Callahan RJ ; Potsaid MS ; Pendergrass HP
AU - Neel HS
3 TI - New technetium-99m skeletal-imaging radiopharmaceutical. 1-Hydroxyethylidene-1,1-disodiumphosphonate-technetium-99m complex (technetium-99m-HEDSPA)
SO - Radiopharm. Label. Compounds, Proc. Symp.: VOL 1,, 1973, P79-92
JC - 28UDA

Appendix 2
(page 2 of 5)

AB - CBAC COPYRIGHT: CHEM ABS the synthesis of 1-hydroxyethylidene-1,1-disodium phosphonate MeC(OH) P(O) (OH)ONa 2 99Tcm (HEDSPA is described. (7414-83-7 1-hydroxyethylidene-1,1-disodium phosphonate) (14133-76-7 Technetium 99) the compd. has a min. lethal dose in mice of 0.2 g/kg. a scanning dose of 0.5 mg is recommended for humans. the compd. was used in approx. 1000 persons for bone scanning without adverse effects, is easily synthesized, and has good chem. stability.
RN - 7414-83-7, 14133-76-7

SI - CA/082/026764V
AU - Vasilenko MM ; Zvezdai VI ; Kolodub FA
4 TI - Toxic action of mononitroaniline isomers
SO - Gig. Sanit.; ISS 8, 1974, P103-4
LA - Russ
JC - GISAA
AB - CBAC COPYRIGHT: CHEM ABS when administered orally to rats, the LD50 values of o-nitroaniline, m-nitroaniline, and p-nitroaniline were 3.52, 0.9, and 1.41 g/kg, resp. (88-74-4 o-Nitroaniline) (99-09-2 m-Nitroaniline) (100-01-6 p-Nitroaniline) when administered at 1/2 LD50, the m-, but esp. p-isomer caused significant increases in the levels of MetHb and SfHb in the blood. o-isomer showed hepatotropic properties. all isomers ha a skin-resorptive effect. exposure of rats to the p-isomer at 5 mg/m3 for 5 hr daily during 4 months caused a decrease inthe Hb level and erythrocyte count in the blood. the hemotoxic effect of the o-isomer was less pronounced.
RN - 88-74-4, 99-09-2, 100-01-6

SI - CA/080/128157A
AU - Loiseau G ; Millischer R ; Berthe G ; Donadieu AM ; Lohier P
AU - Marquet JP
5 TI - Phosphorylated biguanide. Benfosformin (JAV 852). I. Hypoglycemic and antidiabetic properties
SO - Arzneim.-Forsch.; VOL 23, ISS 11, 1973, P1571-6
LA - Fr
JC - ARZNA
AB - CBAC COPYRIGHT: CHEM ABS the hypoglycemic activity of benfosformin JAV 852, PhCH2NHC(:NH)NHC(:NH)NHP(O)(OH)OH)ONa (I), which was more marked in diabetic rats than in normal ones, was comparable to that of phenformin and 2-3 times as strong as that of metformin. (51287-66-2 Benfosformin) (114-86-3 Phenformin) (657-24-9 Metformin) benfosformin hypoglycemic antidiabetic
RN - 51287-66-2, 114-86-3, 657-24-9

SI - CA/080/103873T
AU - Loiseau G ; Millischer R ; Berthe G ; Donadieu AM ; Lohier P
AU - Marquet JP
6 TI - Phosphorylated biguanide. Benfostormin (JAV 852). II. General pharmacological properties
SO - Arzneim.-Forsch.; VOL 23, ISS 11, 1973, P1576-83
LA - Fr
JC - ARZNA

Appendix 2
(page 3 of 5)

AB - CBAC COPYRIGHT: CHEM ABS the hypoglycemic and antidiabetic benfosformin J&V 852, PhCH2 NHC(:NH) NHC(:NH) NHP(O) (OH)2 OH (I) had a high safety margin and was less toxic than phenformin (II), esp. on i.v. administration in mice and rats. (51287-66-2 Benfosformin) benfosformin hypoglycemic antidiabetic
RN - 51287-66-2, 834-28-6

SI - HEEP/73/00668
AU - EARL FL ; CURTIS JM ; BERNSTEIN HN ; SMALLEY H E JR
7 TI - Ocular effects in dogs and pigs treated with dichloran (2,6-dichloro-4-nitroaniline).
SO - FOOD COSMET TOXICOL; 9 (6). 1971 819-828
JC - FCTXA
AB - HEEP COPYRIGHT: BIOL ABS. Beagle dogs and miniature swine were fed dichloran (2,6-dichloro-4-nitroaniline), a fungicide, at levels of 0.75, 6.0, 24, 48 or 192 mg/kg/day in the diet for periods of 50-306 days. Corneal opacities appeared in the eyes of dogs given the 24- or 48-mg levels in 53-104 days in animals exposed to sunlight. Dogs unexposed to the light or with one eyelid sutured in the closed position failed to develop lesions in the unexposed eye or eyes. Slit-lamp examinations revealed that the corneal changes were located in the anterior corneal stroma just below the epithelium. Lens damage was confined to the central anterior cortical areas, giving a circular plaque appearance. These lesions were not reversible when the compound was withdrawn from the diet. Paraffin sections of the damaged corneas of dogs showed, when stained with hematoxylin and eosin, small yellow globules associated with the superficial corneal stromal-cell nuclei. Frozen sections stained with Oil Red O and toludine blue revealed the globules as light-to-dark orange droplets. These droplets were more numerous in the group given 48 mg/kg/day but could also be observed in the groups given 6.0 and 0.75 mg/kg/day. The eyes of swine were unaffected by the feeding of dichloran at the dietary levels that were fed to dogs. Heinz bodies were present in the red blood cells of both dogs and swine given dichloran. Other toxic manifestations were not present in either species, except in the group of dogs given 192 mg/kg/day.
RN - 99-30-9

SI - CA/77/148145
AU - Evstatieva MM
8 TI - Data on the toxicity of acetoacetic acid p-chloro-O-nitroaniline-4-carbamoylanilide
SO - Gig. Primen., Toksikol. Pestits. Klin. Otr; VOL No. 9,, 1971, P351-6
LA - Russ
JC - D8MMY
AB - CBAC COPYRIGHT: CHEM ABS acetoacetic acid p-chloro-O-aniline-4-carbamoylanilide (I) (sic) (10 mg/kg, orally) decreased blood catalase, riboflavin, and SH group concn., and increased SH concn. in the protein fraction of the liver of mice and rats. (036894801 Acetoacetic acid p-chloro-o-nitroaniline-4-carbamoylanilide) (009001052 Catalase) (000083885 Riboflavin) when given to rats as 96 doses

Appendix 2
(page 4 of 5)

of 500 mg/kg, I caused an increase in hippuric acid secretion and in hepatic protein SH content without affecting blood constituents or the liver nonprotein fraction. (000495692 Hippuric acid)
RN - 83-88-5, 495-69-2, 9001-05-2, 36894-80-1

SI - CA/77/148142
AU - Evstatieva MM
9 TI - Toxicity of acetoacetic acid nitrocarbamoylanilide derivatives based on experimental tests
SO - Gig. Primen., Toksikol. Pestits. Klin. Otr; VOL No. 9,, 1971, P356-60
LA - Russ
JC - D8MMY
AB - CBAC COPYRIGHT: CHEM ABS acetoacetic acid m-nitro-p-aniline-4-carbamoylanilide, acetoacetic acid o-nitroaniline-4-carbamoylanilide, and acetoacetic acid p-chloro-o-nitroaniline-4-carbamoylanilide (in 96 doses of 500 mg/kg, during 120 days) caused changes in mice respiratory enzymes, indicative of their toxicity, and induced temporary changes in hemoglobin concns. I also caused leukopenia. (036894787 Acetoacetic acid m-nitro-p-chloroaniline-4-carbamoylanilide) (036894798 Acetoacetic acid o-nitroaniline-4-carbamoylanilide) (036894801 Acetoacetic acid p-chloro-o-nitroaniline-4-carbamoylanilide)
RN - 36894-78-7, 36894-79-8, 36894-80-1

SI - CA/77/096794
AU - Jenner S ; Netter KJ
10 TI - Inhibition of microsomal drug metabolism by SKF 525-A 2-diethylaminoethyl 2,2-diphenylvalerate
SO - Biochem. Pharmacol.; VOL 21, ISS 14, 1972, P1921-7
JC - BCPCA
AB - CBAC COPYRIGHT: CHEM ABS inhibition of mouse liver microsomal O-demethylation of p-nitroanisole and N-demethylation of N-monomethyl-p-nitroaniline (I) by 2-diethylaminoethyl 2,2-diphenylvalerate-HCl (SKF 525-A) (II) was changed from noncompetitive to competitive by benzene recrystn. of II. - (000100174 p-Nitroanisole) (000100152 N-Monomethyl-p-nitroaniline) (000062680 2-Diethylaminoethyl - 2,2-diphenylvalerate hydrochloride) (000071432 Benzene) benzene - produced no chem. alteration of the II mol. that could be - detected.
RN - 62-68-0, 71-43-2, 100-15-2, 100-17-4

SI - CA/77/070274
AU - Dobre V
11 TI - New di(2-chloroethyl)aminophosphoric acid derivatives with antitumoral activity
SO - Farmacia (Bucharest); VOL 20, ISS 4, 1972, P229-34
LA - Rom
JC - FRMBA
AB - CBAC COPYRIGHT: CHEM ABS IOB XXX Na-O-benzoyl bis(2-chloroethyl)aminophosphate (ClCH2CH2)2NP(O)(ONa)OBz, and to a lesser degree IOB XXXI di-Na

Appendix 2
(page 5 of 5)

bis(2-chloroethyl)aminophosphate (ClCH2CH2)2NP(O)(ONa)2 inhibited the growth of various exptl. tumors in rats and mice. (014451377 IOB XXX) (035763112 IOB XXXI) the growth of Jensen tumor in rats was completely inhibited by 40 mg IOB XXX/kg/day and 50 mg IOB XXXI/kg/day administered for 14 days. the LD50 values for IOB XXX and IOB XXXI administered i.v. to mice were 417 and 500 mg/g, resp. the compds. had little effect on hematopoiesis in mice.

RN - 14451-37-7, 35763-11-2

* * * * E N D O F O F F L I N E P R I N T * * * * *

Monsanto

FROM (NAME & LOCATION) Dept. of Medicine & Environmental Health

DATE: July 7, 1976

SUBJECT:

REFERENCE:

TO Distribution

cc: George Roush, Jr., M.D.
J. T. Garrett
G. J. Levinskas
D. L. Eby
P. O. DeGarmo
E. Tillman, M.D.
J. H. Spraul, M.D.
F. R. Johannsen
P. L. Wright
J. Laveglia
M. Stevens

The attached listing shows current or planned long-term studies of materials of direct interest to Monsanto.

The most complete reference for worldwide information (World Health Org.-IARC) is published at about six to nine month intervals and we will plan to issue updates to our listing accordingly. However, other lines of communication, as indicated by the attached references, will result in published and unpublished information which will be summarized on a quarterly basis. Reports and technical papers will be distributed as obtained.

Additional information concerning these studies is, in many cases, available. This includes specific location and names of principal investigators. Let us know if you wish to know more details.

C. Elmer

mo
Att.

CHEMICALS OF INTEREST TO MONSANTO

UNDER TEST FOR CARCINOGENICITY (JULY 1976)

MATERIAL	SPONSOR	TYPE TESTING*	STATUS**	(see P REF.
Acetaldehyde	TNO	Inhal., i. tr. (H)	Partially compl. (publ. in part, see p. 5.)	(5)
Acetone	NCI	Skin & Ingest.(M)		(1)
Acetophenetidin	JAP.	p.o.-diet (R) (M)	Just started	(5)
	NCI	p.o.-diet (M)	Complete	(5)
Acetyl Salicylic Acid	JAP.	p.o.-water (R)	Just started	(5)
	JAP.	p.o.-diet (M)	In progress	(5)
Acrolein	TNO	Inhal. (H)	Histology in progress	(5)
	NCI	Inhal. (H)	In progress	(5)
Acrylonitrile	MCA	Inhal. & Ingest.	Six mos. report due 8/76	(2)
	Europ.	" "	Maltoni-status unKnown	(3)
Acrylic/Methacrylic Acid	duPont	Inhal.	In progress	(3)
	R & H	"	In progress	(3)
Allyl Chloride	MCA		To be started	(2)
	NCI	Gav. (R,M)	Report due	(1)
Ammonium Chloride	NCI	p.o.-water (M)	Completed	(5)
Aniline	NCI	Ingest. (R,M)		(1)
Arsenic	NCI	i.m.-inj. (R)	Completed	(5)
Benzene	API	Inhal.	In progress	(4)
Benzyl Salicylate	NCI	i.p.-(M)	Completed	(5)
Butadiene	IISRP		Report issued	(3)
γ-Butyrolactone	France	s.c.,sk.,i.g.(M) p.o.-diet	Histology in progress	(5)
Cadmium	NCI	i.m.-inj. (R)	Completed	(5)
		i.thor.inj. (M)	Completed	(5)
Caffeine	JAP.	p.o.-diet (R)	In progress	(5)
	JAP.	p.o.-water (R)	In progress	(5)
	UK	p.o.-water (R)	In progress	(5)
	NCI	i.p.-(M)	In progress	(5)
Calcium Chromate	NCI	i.m.-inj. (R)	Completed	(5)
Carbon Disulfide	Australia	Inhal. (M)	In progress	(5)
	NCI			

MATERIAL	SPONSOR	TYPE TESTING*	STATUS**	(see P. 4) REF.
Carbon Monoxide	NCI	Gav. (R,M)	In progress	(1)
Chlorine				
Chlorobiphenyl	NCI	p.o.-diet (R)	In progress	(1)
Chloroform	NCI	i.p.-(M)	In progress	(5)
Chloroprene	IARC	p.o.-(R)	Should be complete	(3)
Chromic Oxide	NCI	i.m.-inj. (R)	Completed	(5)
Cobaltous Oxide	NCI	i.trach. s.c. & i.p.inj.(H)	Completed	(5)
p-Dichlorobenzene	JAP.	p.o.-diet. (M)	In progress	(5)
Dichloroethyl ether	Neth. NCI	p.o. (R) i.p. (M)	In progress In progress	(5) (5)
Dicyclopentadiene	NCI	i.m.-inj. (R)	Completed	(5)
l-Dopa	NCI	i.p. (H)	In progress	(5)
Epichlorohydrin	NCI MCA	Inhal. & p.o.-(R) " "	In progress To complement NCI study	(5) (2)
Ethylene	CIIT	Inhal. (R)	Begun 3/76	(7)
Ethylene Dichloride	MCA	Inhal. (M & R)	Begun 2/76 (Maltoni)	(2)
	NCI	i.p. (M)	In progress	(5)
	NCI	i.g. (R,M)	In progress	(5)
Ethylene Oxide	CIIT		To be funded	(6)
Formaldehyde	CIIT NCI	Inhal. (H)	To be funded Histology in progress	(6) (5)
Hexane	CIIT		To be funded	(6)
Hexachlorobutadiene	Dow	Ingest.	Report about to issue	(7)
Maleic Anhydride	CIIT		To be funded	(6)
Mercury	NCI	i.m.-inj. (R)	Completed	(5)
Methyl Parathion	NCI	s.c. (R)	In progress	(5)
MOCA (4,4'-methylene 2-chloroaniline)	UK NCI	p.o.-diet (H) p.o.-diet (R,M)	In progress In progress	(5) (1)

MATERIAL	SPONSOR	TYPE TESTING*	STATUS**	(see P. REF.
Morpholine	NCI	p.o.-diet (R)	In progress	(5)
Nitrilotriacetic Acid	NCI	p.o.-diet (M,R)	Report in prep.	(5)
B-Nitrostyrene	NCI	p.o.-diet (M,R)	Histology in progress	(5)
Parathion	France	p.o.-diet (R,M)	In progress	(5)
	NCI	p.o.-diet (R,M)	Awaiting pathology	(5)
Pentachlorophenol	Dow	Ingest. (R)	In progress	(7)
Petrochemicals (Petroleum Hydrocarbons)	API	Mortality	Report due	(4)
		Tumor Registry	In progress	(4)
		Solvent Mixt.	To be started	(4)
		Metabolism Studies	In progress	(4)
		Skin Carcinogen.	In progress	(4)
Phenol	CIIT		To be funded	(6)
	NCI	Inhal. (H)	To be planned	(5)
	NCI	p.o.-water (R)	To be planned	(5)
	NCI	p.o.-water (M)	In progress	(5)
Phthalic Anhydride	NCI	p.o.-diet (M,R)	Pathology in progress	(5)
Phthalimide	NCI	p.o.-diet	In progress	(5)
Pivalolactone	NCI	o.g.- (R,M)	In progress	(5)
Polychlorinated biphenyls	Israel	p.o.-water (R)	In progress	(5)
	NCI	p.o.-diet (M,R)	Completed (publ. in part)	(5)
	NCI	p.o.-diet (R)	Histopathy in progress	(5)
Resorcinol	NCI	Subcut. inj. (R)		(1)
	NCI	Skin (Rabb.)	Completed	(5)
Sodium Benzoate	JAP.	p.o.-diet (R)	In progress	(5)
Sorbic Acid	UK	p.o.-diet (M,R)	Compl. in press	
Styrene	NCI	Gav. (R,M)	Histology completed	(5)
	MCA	3 Generation Studies	In progress 18 mo.Inhal. report OK	(2)
	France	p.o. & i.g. (M,R)	In progress	(5)
	NCI	Inhal. (R)	In progress	(5)
Styrene Oxide	France	p.o. & i.g. (M)	In progress	(5)
Tetrachloroethylene	NCI	i.p. (M)	In progress	(5)
	NCI	Inhal. (R)	Histology in progress	(5)
	NCI	i.g. (M,R)	In progress	(5)
Titanium Dioxide	NCI	p.o.-diet (M,R)	In progress	(5)
	NCI	i.trach. (H)	Completed	(5)

MATERIAL	SPONSOR	TYPE TESTING*	STATUS**	(see P REF.
Toluene	CIIT	Inhal. & Ingest.	Begun 3/76	(7)
Toluene Sulfonamides	JAP.	p.o.-diet (R)	Histology in progress	(5)
	CAN.	p.o.-diet (R)	In progress	(5)
Trichloroethylene	MCA	Inhal. (M,R)	Begun 12/75	(2)
	NCI	i.g. (M,R)	Paper in prep.	(5)
	NCI	sk.,s.c.,i.g.(M)	Just started	(5)
Triphenylphosphate	NCI	i.p. (M)	In progress	(5)
Urea	NCI	p.o.-diet (M,R)	Histopathology completed	(5)
Vegadex	NCI	p.o.-diet (M,R)	In progress	(5)
Vinyl Bromide	NCI	sk. & s.c. (M)	In progress	(5)
	NCI	i.g. (R)	In progress	(5)
Vinylidine Chloride	France	p.o. (M,R)	In progress	(5)
	NCI	p.o.-water (R)	In progress	(5)
	NCI	Inhal. (R)	In progress	(5)
	MCA	Inhal.	Compl. (18 mos.)- Pathology incompl.	(2)
		Ingest. (R)	Almost completed	(2)

*Type Testing Abbreviations:

M = Mouse
R = Rat
H = Hamster
inj. = injection
i.p. = intraperitoneal
i.v. = intravenous
i.m. = intramuscular
i.g. = gavage
p.o. = oral
sk. = skin
i.trach = intratracheal

**Status:

Where current status is known, dates are given. When completion is indicated, no reports are known to have been published except where shown.

Status updates will be distributed when information available.

References:

1. National Cancer Institute. List of Chemicals being tested under Bioassay Program.(6/76)

2. Personal communication.

3. SPI listing of studies.

4. API list of Studies underway (1975)

5. IARC (World Health Org.) March 1976 Information Bull. #6"Survey of Chemicals tested for Carcinogenicity."

6. CIIT Brochure May 1976.

PUBLISHED STUDIES:

Acetaldehyde: Feron, V. J. & Kruysse, A.

a.) Acute subchronic and chronic inhalation toxicity studies. (p. 63)

b.) Acute subchronic and chronic studies on acetaldehyde instilled intratracheally. (p. 82.)

in: Experimental Lung Cancer studies in Syrian golden hamsters. Central Inst. for Nutrition & Food Res. TNO, Zeist. (1975)

Polychlorinated Biphenyls: Aroclor 1254
J. Nat'l. Canc. Inst. 53, 547 (1974)

Aroclor 1260
J. Nat'l. Canc. Inst. 54, (1975)

Sorbic Acid: BIBRA Report No. 1973/9

BIBRA Report No. 1975/8

Monsanto

MONSANTO COMPANY
DEPARTMENT OF MEDICINE & ENVIRONMENTAL HEALTH

TOXICITY INFORMATION

TOXICITY INFORMATION ON: SANTICIZER® 409 Plasticizer

TOXICITY

When SANTICIZER 409 was administered to rats, the acute oral LD_{50} was found to be greater than 50.0 grams/kilogram. All rabbits receiving a continuous 24-hour dermal application of SANTICIZER 409 survived the highest dosage tested (10.0 grams/kilogram). Thus, SANTICIZER 409 is considered to be practically non-toxic by ingestion in single doses and by single dermal applications.

When 0.1 ml. of undiluted SANTICIZER 409 was placed into the conjunctival sac of the rabbit eye, a slight degree of irritation resulted. The average maximum score, recorded 1 hour after treatment, was 7.3 on a scale of 110.0. All eyes had regained a normal appearance 72 hours after they were dosed.

No irritation resulted after SANTICIZER 409 was held in continuous 24-hour contact with intact rabbit skin.

In a 4-day static fish toxicity study using fingerling rainbow trout and bluegill, the SANTICIZER 409 96-hour LD_{50} was calculated to be 100 parts per million and 125 parts per million, respectively. On this basis, SANTICIZER 409 is considered to possess a relatively low order of toxicity to both freshwater fish species.

HANDLING PRECAUTIONS

SANTICIZER 409 appears to possess no acute toxicologic properties which would require special handling other than the good hygienic practices employed with any industrial chemical.

5/7/76
Y-57-35
BT-74-55

TESTS USED TO EVALUATE SAFETY OF A PRODUCT

Introduction - The methodology used to test a chemical or drug for various pharmacologic and pathologic effects has developed gradually. Some of the tests are general in their scope and others are very specific. It is recognized that all exposure results in some absorption into the body. Safety can be managed by keeping exposure small when compared to the toxic dose.

An underlying assumption in animal testing is that the response of the animal is a reliable guide to at least the qualitative response to be expected in man exposed to the chemical. Where a cause-effect relationship can be established readily, such as tissue injury or death resulting from one or a few doses of a chemical over a short period of time, animal test data provide a reasonably good basis for predicting effects in man following short exposures. When there is a considerable time lapse between dosing and the observed effect, or when the effect is observed only after prolonged, repetitive treatment with a chemical, the interpretation of animal test data presents varying degrees of difficulty. These chronic effects, carcinogenicity, reproductive impairment, mutagenicity, may result from quantitative or qualitative differences in absorption or metabolism and the nature of the response may be affected by degenerative changes resulting from aging of the animals. Consequently, their cause-effect relationship is not always clearly established. This necessitates detailed observations on large numbers of animals and the integration of data from several experiments to develop an understanding of how a chemical could, or could not, produce the observed effect. Specific comments on individual tests in the screening protocol follow. Adverse findings in any one test could necessitate further studies to determine their potential significance as human health or environmental hazards.

Experimental Toxicological Testing

Acute Toxicity and Irritation Testing

--These tests are sufficiently specific, standardized, and widely used that the results are usually well accepted.

--They serve as basis for labeling and safe handling procedures.

--The fish acute toxicity tests are not as well standardized but they are a useful predicter of dangerous water concentrations.

--Mutagenic potential can be detected by bacterially screening. The interpretations of such results is difficult, as are all mutagenic test systems.

Biodegradation

--This testing will determine whether bacteria can metabolize the chemical. Such data gives good indication that the product will not accumulate in the environment.

Metabolism

--These studies are not standardized but a great deal of information is obtained quite inexpensively.

--The possibility of accumulation is evaluated and possible accumulation in one organ or another can be detected.

--Species differences are great and extrapolation to man must be made very cautiously.

Sub-Acute Toxicity

--These studies are of paramount importance because, together with cancer, mutagenicity, and teratology, they represent subjects at the forefront of public health concern today.

--Such testing will establish the target organ, at least for the test animal.

--It will establish the safety factor between the highest no effect and lowest effect level.

--It will also evaluate absorption from the GI tract and the hazard of inhalation.

Reproductive Effects

--The significance of the dominant lethal test has not been established. It is a means of evaluating a concern of public health effects.

--Rabbit teratology studies are better standardized and can be useful, but studies are often equivocal rather than discriminating.

Chronic Toxicity

--Methodology for cancer testing has not been standardized but does involve lifetime testing using more animals.

--Negative studies are most useful, but because of many factors, statistical findings are difficult to interpret.

These tests should be performed on all products unless there is a specific reason for not doing them--such as availability of comparable data from other sources. Most of these will be performed on rodent species, although larger animals could be used with certain materials or in special circumstances.

	Acute toxicity and irritation tests	
$500	(Rat oral LD_{50} (Rabbit dermal LD_{50} (Rabbit skin irritation (Rabbit eye irritation (Rat inhalation (vapor, dust, aerosol)	
$250	Fish acute toxicity	
$150	Mutagenicity in microorganisms	
	Biodegradation	
$2000	Semi-continuous activated sludge (SCAS)	
	Metabolism and target organ response	
$20,000	Distribution, storage, excretion Detection of specific urinary metabolite	
	Subacute toxicity	
$25,000	Oral Dermal Inhalation	(Cost will depend on route of exposure and duration)
	Reproduction effects	
$5,000	Teratology	
$8,000	Mutogenicity	
	Chronic toxicity, carcinogenicity screen	
$75,000 to $250,000	Oral Dermal Inhalation	(Cost will depend on route of exposure and duration)

Co.	PRODUCTS CURRENTLY ON LONG-TERM TESTS 1974	1975	1976	CANDIDATES FOR STUDY
MAP	AVADEX AVADEX BW	Monochloro-toluene RANDOX Rice herbicide ROUNDUP metabolite VEGADEX	Aniline, 2,6-diethyl- N-isopropyl- Chloroacetyl chloride Chloropropenes, di-, tri-, tetra- Monochlorotoluene	Chloropropanes, tri-, tetra-, penta- * Epichlorohydrin MACHETE Root worm insecticide Soybean herbicide
MCP	-	-	-	CYCLESAFE
MIC	SANTOFLEX 13 SANTOFLEX 77	Na & Ca salts, Builder M SANTOSOL 200 TCC Tolyl xylyl sulfone	Benzyl chloride Capacitor fluid - MCS 1238 DEQUEST 2000 Monochlorobenzene Phthalimide SANTICIZER 154 SANTICIZER 160 SANTOGARD PVI Synthetic fatty acid	Benzylated C_9 aromatics * Dichlorobenzene, o-, p- ** Maleic anhydride NITROL Pentachlorophenol SANTOSOL 100 SANTOSOL 340
MP&P	* Acrylonitrile * Styrene * Vinyl chloride * Vinylidene chloride	-	*** Butadiene	** Phenol Glutaric acid
MT	-	Dimethyl acetamide	Hexamethylene-diamine Sodium methallyl sulfone * Vinyl bromide	-
NED	-	Hypocholesteremic agent	- -	-

* MCA task force
** Chemic Industry Institute of Toxicology
*** International Institute Synthetic Rubber Produce.s

RSV 00104888

Monsanto

Appendix 7

FROM (NAME & LOCATION) Dept. of Medicine & Environmental Health - G.J. Levinskas, A2SG

DATE: August 27, 1976 CC:

SUBJECT: Aquatic Toxicity Test Facilities

REFERENCE:

TO George Roush, Jr.

Initially, the proposed Biological Research Laboratory was to contain facilities for aquatic toxicity tests. The subsequent decision to locate the laboratory near Washington University's Medical School resulted in increased costs and raised questions about providing water suitable for aquatic tests. In order to maintain momentum, it was decided to proceed without the aquatic areas.

Since then, I have queried others regarding their opinions and/or experiences at attempting to dechlorinate a municipal water supply. From their replies, I conclude that dechlorination can provide water of sufficient quality for many fish studies. There is concern about the quality of water for testing certain types of materials and for tests with invertebrate species.

I recommend that aquatic toxicity test facilities be established at St. Peters. That location:

a) has well water suitable for all types of aquatic studies,
b) provides space for outdoor fish ponds to study seasonal effects on aquatic species,
c) provides space for "pilot plant" biodegradation studies (septic tanks, small-scale sewage treatment plants),
d) permits economies in construction and operation, and
e) alleviates crowding in the Research Center.

Brief citations in support of these advantages follow. Well water from St. Peters currently is used in N building for aquatic studies. Outdoor ponds would not be practical in St. Louis. Scaled down versions of septic tanks or sewage treatment plants would permit field studies of biodegradability under various climatic conditions. This would be a one-story building with less frequent air changes, and a large part of the air could be recirculated. If the aquatic toxicity facility includes biodegradation studies now being performed at Creve Coeur, this would permit conversion of the latter space to other uses. This could require purchase of additional analytical instruments.

Finally, it is recommeded that the aquatic toxicity test facility be a part of DMEH.

George J. Levinskas

Monsanto
FROM (NAME & LOCATION) Dept. of Medicine & Environmental Health - G.J. Levinskas, A2SG

DATE: June 4, 1976

cc J.T. Garrett - A2SG
S.A. Roberts - A2SC
B. W. Eley - A2SC

SUBJECT: NTA: Recommended Exposure Guidelines

REFERENCE: SAR to GR, 6/1/76

TO

G. Roush, Jr.,M.D.
A2SA

Suggested exposure guidelines for air levels of NTA are:

a) 1.0 mg/m^3 for an 8-hour TWA, and
b) 2.0 mg/m^3 for a 15-minute excursion. Excursions should be limited to no more than 2 per 8-hour day.

Concurrent analyses of urine for NTA would be desirable. They would afford an estimate of the proportion of the inhaled amount which appears in the urine. If the suggested TWA is not exceeded, urinary output of NTA should be no more than 10 mg in 24 hours.

A judgement that around 0.1 mg/kg/day is "safe" underlies this recommendation. That judgement is based upon the following considerations.

A lifetime feeding study with the sodium salt of NTA shows that ~2000 ppm is a "no-effect" level in rats. Using A.J. Lehman's conversion factor, that translates into a dosage of 100 mg/kg. Application of a safety factor of 1000 provides an estimated safe dosage of 0.1 mg/kg/day.

Similar studies with mice resulted in a "no-effect" level of 2500 ppm. This calculates out to a dosage of 375 mg/kg which leads to an estimated safe dosage of 0.375 mg/kg.

The adequacy of a 1000-fold safety factor for a potential carcinogen can be debated. However, urinary tract tumors in the rat are rare in the absence of concretions. The reports we have received do not indicate whether or not chelates of NTA had formed and deposited in the urinary tracts of the test animals. If there were chelates, the safe level would be any level below which deposits occurred. In addition, it is not likely that there will be complete absorption of the entire amount inhaled. Thus, the safety factor may be greater than indicated by the calculations discussed above.

A man breathes 10m^3 of air during an 8-hour working day. At a

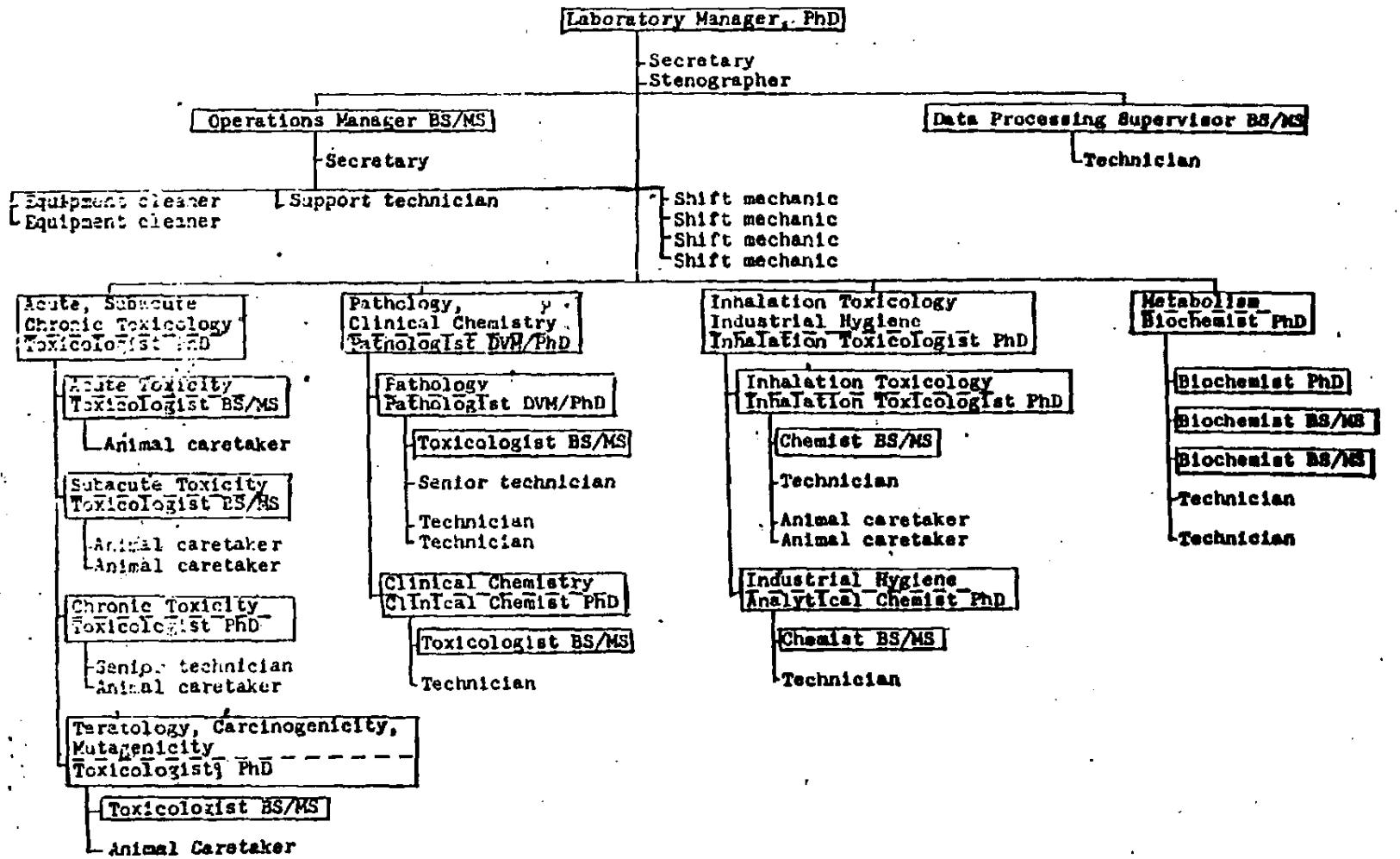
concentration of 1.0 mg/m^3, if he inhaled and retained all of the NTA, he would receive a total dose of 10 mg. For the hypothetical 70-kg man, this would be a dosage of 0.14 mg/kg.

In order to control the total dose to the man, it will be necessary to avoid NTA intake by other routes. Thus, food or beverages should not be brought into or consumed in the work area, and all employees should wash their hands thoroughly before eating or drinking and at the end of the work shift.

George J. Levinskas

/bkp

PROPOSED MANNING TABLE ENVIRONMENTAL HEALTH LABORATORY



Environmental Health Laboratory

Staffing as of End of 1977

*Lab Manager (PhD)	1
Secretary	1
*Operations Manager (BS/MS)	1
*Data Processing Supervisor (BS/MS)	1
Toxicologist (PhD)	1
Senior technician	1
Clinical chemist (PhD)	1
*Inhalation Toxicologist (PhD)	1
Chemist (BS/MS)	1
Biochemist (PhD)	1
Biochemist (BS/MS)	1
Total	11

*Critical specialist. Early hiring needed.

Environmental Health Laboratory

Staffing as of End of 1978

	Have	Hire	Total
Lab Manager (PhD)	1	-	1
Secretary	1	-	1
Operations Manager (BS/MS)	1	-	1
Secretary	-	1	1
Equipment cleaner	-	2	2
Support technician	-	1	1
Shift mechanic	-	4	4
Data Processing Supervisor (BS/MS)	1	-	1
Toxicologist (PhD)	1	-	1
Toxicologist (PhD)	-	2	2
Toxicologist (BS/MS)	-	2	2
Senior technician	1	-	1
Animal caretaker	-	3	3
Pathologist (DVM/PhD)	-	1	1
Clinical chemist (PhD)	1	-	1
Toxicologist (BS/MS)	-	1	1
Senior technician	-	1	1
Technician	-	1	1
Inhalation Toxicologist (PhD)	1	-	1
Inhalation toxicologist (PhD)	-	1	1
Analytical chemist (PhD)	-	1	1
Chemist (BS/MS)	1	1	2
Technician	-	1	1
Animal caretaker	-	1	1
Biochemist (PhD)	1	-	1
Biochemist (PhD)	-	1	1
Biochemist (BS/MS)	1	1	2
Technician	-	1	1
Grand Total	11	27	38

Environmental Health Laboratory

Staffing as of End of 1979

	Have	Hire	Total
Lab Manager (PhD)	1	-	1
Secretary	1	-	1
Secretary	-	1	1
Operations Manager (BS/MS)	1	-	1
Secretary	1	-	1
Equipment cleaner	2	-	2
Support technician	1	-	1
Shift mechanic	4	-	4
Data Processing Supervisor (BS/MS)	1	-	1
Technician	-	1	1
Toxicologist (PhD)	1	-	1
Toxicologist (PhD)	2	-	2
Toxicologist (BS/MS)	2	1	3
Senior technician	1	-	1
Animal caretaker	3	2	5
Pathologist (DVM/PhD)	1	-	1
Pathologist (DVM/PhD)	-	1	1
Clinical chemist (PhD)	1	-	1
Toxicologist (BS/MS)	1	1	2
Senior technican	1	-	1
Technician	1	2	3
Inhalation Toxicologist (PhD)	1	-	1
Inhalation toxicologist (PhD)	1	-	1
Analytical chemist (PhD)	1	-	1
Chemist (BS/MS)	2	-	2
Technician	1	1	2
Animal caretaker	1	1	2
Biochemist (PhD)	1	-	1
Biochemist (PhD)	1	-	1
Biochemist (BS/MS)	2	-	2
Technician	1	1	2
Grand Total	38	12	50

Appendix 10

Environmental Health Laboratory
Tentative Manning Table - Proposed Expansion

Assistant Laboratory Manager (PhD)	1
Pathologist (PhD/DVM)	1
Histologist (BS/MS)	1
Biochemist (PhD)	2
Biochemist (BS/MS)	2
Microbiologist (PhD)	1
Inhalation Toxicologist (PhD)	1
Inhalation Toxicologist (BS/MS)	2
Toxicologist (PhD)(Carcinogenicity)	1
Toxicologist (PhD)	2
Toxicologist (BS/MS)	6
Secretary	1
Stenographer	1
Shift mechanic	3
Equipment cleaner	2
Senior technician	2
Technician	10
Senior animal caretaker	1
Animal caretaker	10
Total	50

Appendix 11

Aquatic Toxicity Laboratory

Proposed Manning Table

- Senior Aquatic Toxicologist (PhD) 1
  - Secretary 1
  - Aquatic Toxicologist (PhD) 1
    - Aquatic toxicologist (BS/MS)..... 1
    - Senior technician 1
    - Technician 3
    - Fish caretaker 2
  - Biochemist (PhD) 1
    - Senior technician 1

Total 12

PROCESS ENVIRONMENTAL

[redacted]

RSV 0010498

PROCESS ENVIRONMENTAL

The Process Environmental Section's function is to develop, in concert with operating companies, health related surveillance of the environmental effects of plant effluents and emissions and of the appearance of Monsanto's products in the environment resulting from transportation and use. We must develop in-house experts as needed to provide effective liaison among the operating units and staff departments. Considerable effort is needed to follow and hopefully influence legislative developments as well as to be up-to-date on regulations, permits, and trends in enforcement agencies.

Predictions

1. Government regulation will increasingly zero in on specific toxic pollutants - carcinogens leading the parade.

   Politically sensitive areas such as auto transportation controls and urban run-off will not be tackled seriously. Chemical targets are easy to attack, cause limited direct voter antagonism.

   Both government and environmentalists PR programs can effectively exploit public's fear of the unknown.

2. It will be increasingly necessary to explain the facts of risks and benefits to public at large and to employees.

3. Approval for new facilities and for major expansions and modifications will require more detailed and broader scope Environmental Effects Assessment - and thus longer lead times.

4. More specific chemical compounds will be "discovered" in places.

   Analytical techniques will be more precise. Monitoring and sampling by governments will be more intensive.

5. Monitoring and enforcement for chemicals will shift from sanitary engineering parameters toward trace quantity analysis and biological effects determination.

6. Industry's responsibilities will be increased by pressures transferred from municipalities.

   Publicly owned sewage treatment plants can solve their problems by more stringent pre-treatment requirements for industrial users.

   Public water treatment plants can prohibit chemicals in intake water instead of removing them by treatment. Boiled down to issue of using private capital vs.

public funds, decisions will be based on best politics rather than best technical solution.

7. Cost-benefit arguments will be more effective for specific cases than on broad national and industry scope.

   How many local jobs will be affected?

   How will local economic input-output numbers change?

   Impact on local tax revenues.

8. New approaches to our technical-economic decisions will be needed.

   Trade-off situations will occur. If we need to add a pollutant to environment, we must subtract a somewhat greater amount elsewhere.

   If we are allowed .1 mg/l of a certain chemical in plant effluent, what is the best product/process mix?

Questions and Responses

1. Regulation will emphasize specific toxic pollutants. Which ones will have priority?

   Factors in setting priorities will be:

   a. Existing regulation, and regulatory trends.

   b. Known or indicated harm to environment.

   c. Economic significance to Monsanto.

   d. Extent to which measurement or detection is feasible.

   It is expected that priorities will change as new information is developed and control policies are altered. For 1977-78 period, high priority will be on substances presently established for regulation under water and air laws.

   Arsenic
   Mercury
   Cadmium
   Cyanide
   Polycyclic Organic Matter
   Polychlorinated Biphenyls

   Longer term, the suspect carcinogens from established hazardous chemical lists will gain top priority. Among the many on suspect lists, these will be of

most economic significance:

Benzene
Maleic Anhydride
Refractory Organo-Chlorine Compounds

2. Risk/benefit educational programs will be needed.

DMEH must anticipate probable areas of concern. Factors to consider are:

a. Follow on apprehensions from OSHA workplace controls, i.e. when exposure to a substance is stringently controlled in-plant, families and communities will worry about external risks.

b. Publicized chemical "incidents" will focus public apprehension.

c. Our own clinical or toxicological findings will suggest need for information programs.

Typical substances of near-future concern:

Vinyl chloride monomer
Benzene
Arsenic
Dioxins
Nitrosamines

DMEH will be responsible to identify areas where public awareness will be important and to provide assessment of health and environmental risks. Degree of risk will generally be proportional to amounts of substances present or potentially released to environment.

Action should be through Public Affairs group, line organization community programs or well-placed technical or general media publications. DMEH will support such actions with data and suggested strategies.

Information should be developed on benefits and economic impacts vs. risk. DMEH will provide technical information on comparative health and environmental factors for substitute or competitive products or substances.

3. Major new projects will need Environmental Assessment.

It will take time for agencies to decide if full Environmental Impact Statement is required - and more time to complete procedures and hearings if it is. Could stretch start-up date one to two years.

By evaluation of regulatory trends and actual site environmental situation, we should determine what baseline

data will be needed and obtain it as early as possible.

Such actions can include:

Determining existing levels of pollutant in soil, air and water.

Assaying present biota and vegetation conditions.

Projecting ecological changes which would result from proposed projects - both harmful and beneficial.

4. More specific chemical compounds will be discovered in the environment.

We need to anticipate the significance of such discoveries and obtain more complete data where warranted.

DMEH will initiate monitoring in specific cases where there is reason to anticipate the presence of Monsanto's substances.

However, the tremendous efforts and expenditures for worldwide government-sponsored monitoring and analysis cannot be duplicated by private sector.

DMEH will follow results of such monitoring closely and will concentrate on determining the environmental fate and sources of introduction of those discoveries which are significant to Monsanto.

Priority lists for environmental presence and fate determinations will be started in 1977. Initial basis will be screening of data from 117 city drinking water supply analysis by EPA and also the expected ranking of aquatic bio-accumulative substances by EPA research laboratories.

When significant findings emerge, the actions required will be:

To confirm, perhaps duplicate the data.

Evaluate the health and ecological risks.

Determine the sources of introduction of the substance to the environment.

Initiate suggestions for elimination and also for practicable regulations and control.

5. Regulations will shift from sanitary engineering parameters to trace analyses and biological effects.

It will be necessary for DMEH to establish field biological aquatic monitoring expertise and to broaden laboratory aquatic toxicological capabilities.

DMEH has established protocols for aquatic toxicity testing of specific substances under laboratory conditions. These will be translated to on-site, mixed effluent conditions to assist operating plants where EPA is beginning to require such tests.

Field evaluations of receiving waters biological conditions will be conducted to determine the overall effects of our effluents.

The Toxicology section will propose laboratory facilities for aquatic toxicity testing. It is planned that these will include capabilities for testing and evaluation of mixed effluent streams to back up the field work of the Environmental section.

It is probable that regulations will require reduction in toxicity of plant effluents in addition to BOD reductions currently imposed.

Effluent toxicity testing should include ability to determine characteristics of components as well as mixed effluents. From this the process and treatment changes necessary for toxicity reduction can be determined.

Although beyond the current scope of DMEH responsibilities, waste treatment pilot-plant facilities may be required to correct the toxicity conditions determined by the aquatic laboratory work.

It is expected that CRD and Operating Companies will continue to stay at leading edge of state-of-the-art chemical analysis. DMEH does not plan to build analytical expertise in environmental functions.

6. Industry's load will be increased by pressures from municipalities.

Pre-treatment requirements from publicly-owned treatment plants will require point-source removal of specific toxics. The composition of wastes destined for public plants must be characterized. Bio-degradability and aquatic toxicity of composite wastes must then be determined. Selective testing and plans for elimination of damaging effluents must be done before the risk of operational upsets is incurred.

These requirements will be supported by the Environmental Section aquatic monitoring and toxicity testing described in Section 5. The intrinsic features of the public treatment works and the technical ability of its staff will be elements not encountered in our plants which have their own treatment. DMEH will provide consultation and initiate suggestions to the line organizations dealing with the public works. Drinking water plants will require removal of specific toxics from our direct discharges. The organic compounds with high persistence and low bio-degradability are likely to be pinpointed despite satisfactory overall BOD removal. Suspect carcinogens from the list of 77 hazardous chemicals which are now being studied by EPA Effluent Standards group will have priority.

Such requirements will be based on the capability of the municipal plants to handle the toxic chemicals in their systems. We will need to provide more chemical, toxicological and treatability data on our substances. The aim will be to arrive at cooperative technical solutions. Otherwise, we face refusal to accept and be obligated for complete removal in our plants.

DMEH will identify potential chemical problems in the drinking water situations and provide sufficient lead time for the development of solutions or avoidance. The capabilities described in sections 4 and 5 will be utilized:

Monitoring and identification

Toxicity testing

Pilot-plant treatment studies

7. Cost-benefit arguments will be critical to gain local or state approval for expansions or modifications and to continue public acceptance of our presence in the face of probable fears and alarms.

DMEH needs to describe health effects and epidemiological data in understandable terms.

Process Environment Section will prepare yearly priority listing of those chemicals for which we are likely to need to establish a health effects position. At present, no specific new area is identified.

The health effects information, together with economic advantages of jobs, tax revenues, etc., plus evidence of our operational and waste disposal safeguards should be presented to the public in a manner that will provide understanding of the advantages as well as disadvantages of our presence, and of our proposed new projects.

8. New approaches to our technical-economic decisions will be needed.

Capital, energy and operating costs for environmental controls have increased to the point that they are significant factors in business decisions on products and processes.

Governmental cost-benefit analyses, in the few cases where they are required, tend to understate costs and inflate societal benefits.

DMEH should contribute projections of possibilities and probabilities of environmental requirements to be factored into business decisions. These should be based upon our developing specific chemical and toxicological findings and on our presumption of the course of future regulation.

In 1977-78, our direct participation in MCA projects on hydrocarbons-photochemical oxidants standards and regulations will be a major effort. This is typical in that health effects per se cannot be made a major issue. The extreme cost of proposed solutions, with questionable technical basis, would yield minimal health benefits.

DMEH will continue to represent the Company in constructive action on regulatory and legislative issues.

Development of specifics on costs, technical feasibility and economic consequences continues to be on an ad hoc basis with participation of operating company and CED personnel. A more unified system would be desirable as the need for presenting integrated socio-economic positions increases.

Resources Required

This function will continue to be predominantly advisory and consultative.

The technical resources for the most part exist in other parts of the corporation - although expanded effort will be required.

- CED - Technology for pollution treatment, removal and process monitoring
- CRD and Operating Companies - Technology for chemical analysis, treatability and biodegradation and decomposition.

We expect to continue to utilize outside contractors for environmental assessment and monitoring on a project-by-project basis.

Expanded use of MRC - Dayton capabilities will have first priority. It is not planned to build up complete capability in environmentally-related functions with a view to selling it outside, as Carbide has done with its subsidiary, Aquatic Environmental Sciences, or Dow with Hydroscience. If such enterprises were contemplated, it is assumed they would be under MRC or Enviro-Chem.

We do need to establish expertise in aquatic biological monitoring and general aquatic bio-assay techniques. The utilization would be:

1. To obtain source, fate and effects of our substances as they are discovered in the environment.

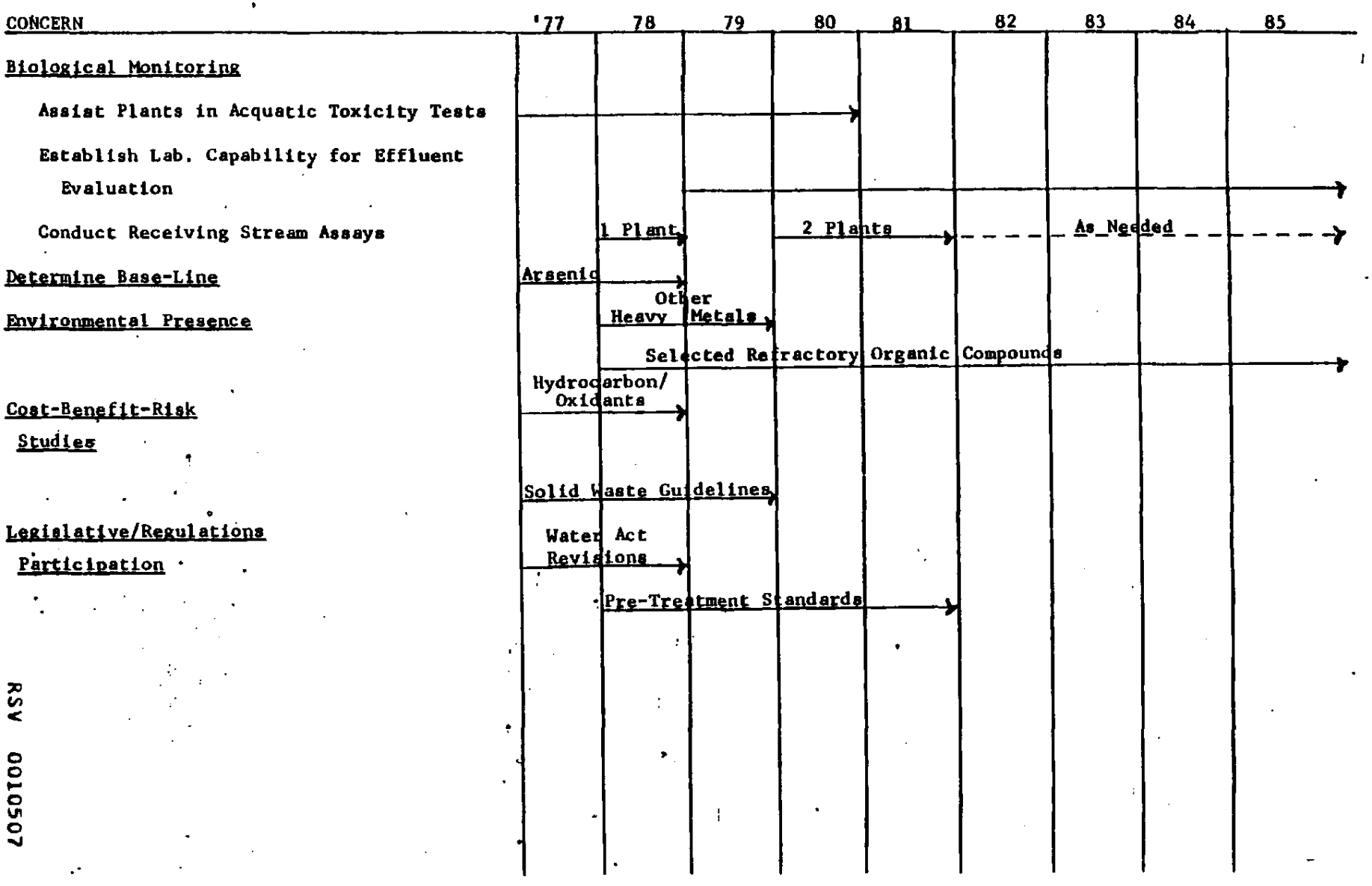
2. To provide guidance to operating plants in aquatic effluent monitoring until such becomes routine.

Although legislative, regulatory and industry association contacts are of a generally continuing maintenance type of activity, it is expected that special projects and task force missions will increase. Where possible, we plan to continue to "borrow" participants from CED, operating companies, etc., but anticipate the need for increased full-time DMEH managerial attention.

It is proposed to add one technical specialist in aquatic monitoring and survey procedures in 1977. When DMEH aquatic toxicological testing laboratory facilities are available (1978?), one full-time laboratory professional should be assigned to process environmental studies to augment the field survey programs.

In 1978, the need for the addition of one environmental engineering specialist is expected for assignment to major, complex projects both with the corporation and with industry-wide study projects. Most contract studies will be for specific product-process areas and should be costed directly to the operating units. Since we expect to preferentially use MRC, there is little advantage in pass-through cost allocation as is done for Toxicology contracts. The DMEH supported contract costs will increase only incrementally.

PROCESS ENVIRONMENTAL PLANS



PROCESS ENVIRONMENTAL RESOURCES

	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986
PERSONNEL											
Professional	1	2	3	3	3	3	3	3	3	3	3
Secretarial	0.5	0.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Capital $1000		10		100		100	5	5	5	5	5