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THE IMPACT ON DOD OF THE TOXIC SUBSTANCES CONTROL ACT

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FOR THE COMMANDER



ANTHONY A. THOMAS, MD
Director
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) There are a number of driving factors which markedly affect the utilization and acquisition of new chemicals within the Department of Defense and throughout the national industrial community. The Toxic Substances Control Act of 1976 and other previous legislations have mandated a complete series of test standards designed to identify chemical hazards and establishing minimum requirements for performing acute, subacute, and chronic toxicity tests, mutagenic effects, teratogenic effects, oncogenic effects and metabolic effects on both flora and fauna. A scheme for obtaining these data, and the relative time and expense necessary to assess chemical hazards is discussed along with case-in-point chemical data on ram jet fuels illustrating potential problem areas of such legislation.		

PREFACE

This technical report was an invited oral presentation by Dr. Kenneth C. Back at the Tenth Annual Environmental Systems Symposium, 16-17 October 1979 by the American Defense Preparedness Association. It was held at Cockran Hall, Charleston Naval Base, Charleston, South Carolina.

THE IMPACT ON DOD OF THE TOXIC SUBSTANCES CONTROL ACT
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There are a number of driving factors which markedly affect the utilization and acquisition of new chemicals within the Department of Defense, and for that matter, throughout the national industrial community. The development of fundamental information on the toxic hazards of DOD used chemicals and the need for understanding the mechanisms of toxic activity in order to establish realistic exposure criteria are increasing exponentially. The driving forces provoking increased emphasis on chemical hazard assessments include the National Environmental Policy Act of 1969, the Clean Air and Water Act of 1970, the Occupational Safety and Health Act of 1970 and the most recent Toxic Substances Control Act of 1976. The latter is one of the most definitive pieces of legislation to date and mandates a complete series of test standards designed to identify chemical hazards from the cradle to the grave and establishing minimum evaluation tests for acute, subacute and subchronic toxicity, mutagenic effects, teratogenic effects, reproductive effects, and metabolic effects on flora and fauna. Table 1 is a much condensed version of the myriad of tests necessary for obtaining information for "Premanufacturing notification to EPA before a new chemical or an old chemical to be used in a new way may be manufactured.

Table 1. HEALTH EFFECTS TESTS
 BASE SET STUDIES (STANDARD TESTS)

ACUTE

Lethality (LC-50, LD-50)
 Primary Eye Irritation
 Primary Dermal Irritation
 Dermal Sensitization

SUBCHRONIC

90 Day Toxicity

Mutagenic and Short Term
 Predictive Oncogenic

Gene Mutation (3 tests)

Bacteria (Ames)
 Insects
 Mammalian Cell Lines
 Mouse Specific Locus

Chromosomal Aberration
 (1 test)

In vivo Cytogenic Damage
 Insect-Heritable Damage
 Rodent Heritable Translocation

REPRODUCTION
 FUNCTION

1 Mammalian Species
 1 Generation $F_0 \rightarrow F_1$
 3 Dose Levels
 30 Animals per dose level

Primary DNA Damage
 (2 tests)

Bacterial DNA Repair
 Unscheduled DNA Repair
 Synthesis in Mammalian
 Mitotic Recombination/Gene
 Conversion
 Sister-Chromatid Exchange

The vast number of tests required together with the possible use characteristics and the physical-chemical properties of the compound represents a large number of manhours and a cost over \$1.5 million. This magnitude of expended resources is to be borne by the manufacturer regardless of the total amount of chemical to be used. Obviously, some consideration of anticipated tonnage must be given since, at the moment, manufacturers of some food additives are required to produce the same kinds and amounts of data as others planning to market multiton quantities. As a matter of fact, in the flavoring and fragrance industry, the total output of all manufacturers in the world represents a quantity of product less than that needed to perform all the research studies required by the various protocols.

In order to perform all the necessary experiments to conform to the requirements, a multidisciplinary approach has been used by the USAF for the past 25 years. The pharmacologist-toxicologist obtains the toxicity parameters such as dose-response curves, pharmacodynamics (effects on organ systems), pharmacokinetics (metabolism of compound as it passes through the body) and possible therapeutics for overexposure. The pathologist and biochemist look at cellular effects while the behaviorist looks at effects on performance. Analysis is made of methods for quantitation and detection in affected personnel and the environment for monitoring purposes, and the effects on the ecology (flora and fauna) must be evaluated.

A scheme for getting these data is outlined in Figure 1. It is obvious that the data necessary to produce good industrial medicine standards and criteria for safe handling take 5-7 years as a minimum. Depending upon use, the cost could escalate to \$10 million for cradle to grave operation.

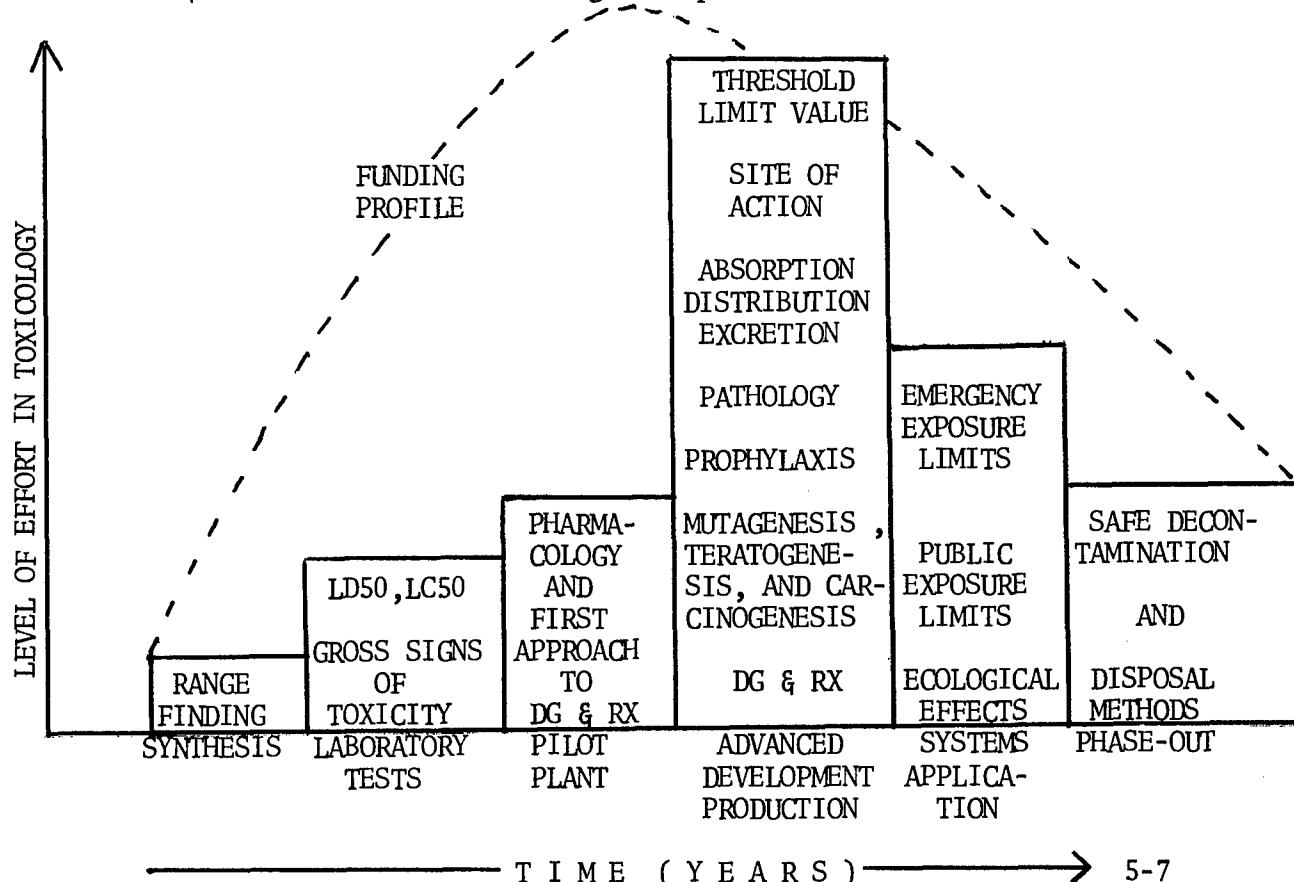


FIGURE 1 - PHASING OF TOXICOLOGY WITH CHEMICAL DEVELOPMENT

Besides cost and the long time it takes to get the data, two disturbing points must be kept in mind. The first involves the strong stand taken by TSCA to establish standards by a process called "generic toxicology." This implies that close chemical congeners possess the same biological properties and may be "lumped" for standard setting. This speeds up the process of setting standards but is completely illogical. For instance ethyl alcohol and methyl alcohol are only different by one carbon. But only methyl alcohol metabolizes to formaldehyde in the body to produce toxicity, while ethyl alcohol when ingested goes to CO₂ and H₂O.

The second disturbing philosophy expounded by the EPA is that there is no dose response curve for an oncogen (tumor producing compound) and therefore one cannot set a standard of exposure for such a compound. This philosophy has no scientific basis in fact. Most toxicologists have shown good dose response relationships for oncogens using laboratory animal models. It is my contention that these models can be used to provide finite standards for man and that the concept of using "lowest detectable amount" as a criterion is costly and wasteful. This is the dilemma facing the nation today when one observes the problems associated with the oncogenic (in animals) compounds such as saccharin, benzene, n-nitrosodimethylamine, chloroform, JP-4 jet fuel (contains benzene), coke oven emissions, et cetera.

A case in point and directly affecting the DOD is shown in the following tables.

Table 2. JP-4 FUEL

ACUTE TOXICITY

Oral	Rat LD Lowest	> 8,000 mg/kg
	Mouse LD Lowest	= 500 mg/kg
6 Hr Inhalation	Rat LC Lowest	> 38 mg/L

EFFECTS

Eye Irritation - Positive
Skin Irritation - Positive

CHRONIC TOXICITY

Exposure Time = 6-8 Months, 6 Hr/Da, 5 Da/Wk

Exposure Concentrations:

JP-4 - 5.0 mg/L (contains 25 ppm Benzene)

JP-4 - 2.5 mg/L (contains 12.5 ppm Benzene)

Benzene - 25 ppm

Animals/Exposure:

6 dogs, 4 monkeys, 50 rats, 40 mice

EFFECTS

JP-4	{	Central Nervous System Depression, Lethargy, Emesis
		↑Red Blood Cell Fragility in Female Dogs at High Dose
		↑Incidence Chronic Bronchitis in Rats
Benzene		CNS Depression, lethargy
JP-4 and Benzene		Oncogenic Response Not Remarkable

Table 2 (Continued)

MUTAGENIC POTENTIAL

Microbial Assay (Ames) - Negative
 Mouse Lymphoma - Negative
 Unscheduled DNA Synthesis - Nonspecific Damage
 Dominant Lethal - Preimplantation Loss (Toxic)
 SUMMARY: No Effect on Fertility
 Minimal Genetic Toxicity
 Negative for Mutagenic Potential

SUGGESTED STANDARD

JP-4 = 2.5 mg/L TLV

REFERENCES

AMRL-TR-74-78, AMRL-TR-76-57, and AMRL-TR-78-24, Wright-Patterson AFB, Ohio

Table 3. TUMOR INCIDENCE IN ANIMALS EXPOSED TO JP-4 OR BENZENE
 FOR SIX MONTHS AND HELD ONE YEAR POSTEXPOSURE

	<u>CONTROLS</u>	<u>25 PPM BENZENE</u>	<u>5.0 MG/L JP-4</u>	<u>2.5 MG/L JP-4</u>
<u>MOUSE TUMORS</u>				
Alveolargenic Adenoma	3/19	6/17	4/16	7/21
Lymphosarcoma	0/19	1/17	1/16	2/21
Mammary Carcinoma	0/19	1/17	0/16	0/21
Hepatoma	1/19	0/17	0/16	0/21
Hematopoietic Tumors	6/19	1/17	4/16	3/21
Thyroid Carcinoma	<u>0/19</u>	<u>0/17</u>	<u>1/16</u>	<u>0/21</u>
TOTAL	10/19	9/17	10/16	12/21
<u>RAT TUMORS</u>				
Mammary	0/15	0/16	1/20	0/18
Thyroid Adenoma	0/15	1/16	0/20	0/18
Pancreatic Islet Cell Adenoma	<u>0/15</u>	<u>1/16</u>	<u>0/20</u>	<u>0/18</u>
TOTAL	0/15	2/16	1/20	0/18

REFERENCE AMRL-TR-76-57, Wright-Patterson AFB, Ohio

These compare the toxicity and oncogenic potential of JP-4 fuel and two ram-jet compounds, RJ-4 and RJ-5. One sees that JP-4 fuel has a relatively low order of acute and chronic toxicity and that animals can accommodate up to 5 mg/liter which contains 25 ppm benzene. Since there were some weight losses noted at that level, we have suggested that for an 8-hr work day, 5-day work week, 30-year working life (Threshold Limit Value, TLV) one could be exposed to 2.5 mg/liter. Note that this amount contains 12 ppm benzene (Table 2). Note also in Table 3 that there were no increases in tumor production between controls and benzene or JP-4 regardless of doses. However, it must also be kept in mind that the TLV for benzene is 10 ppm at gas stations and 1 ppm in rubber factories. So we are saying that 2.5 mg/liter JP-4 is safe. OSHA or EPA probably do not agree, although I can not reconcile a limit of 10 ppm in the gasoline area where there is a potential for 400,000 exposures while in the rubber industry the potential is only 150,000 but the limit is 1 ppm. It would appear that if one were really worried about the leukemogenic effect of benzene at these low levels the TLVs would be the same.

The comparative toxicity of the ram-jet fuels RJ-4 and RJ-5 is found in Tables 4, 5 and 6. As shown, the compounds are extremely odoriferous but not very toxic even at saturation. In the mutagenic potential tests, both show little potential for mutagenic effects. This is an important finding since TSCA rules imply that if any two microbial tests are positive one can expect the compound to be a tumor producer. There are many who claim that the Ames test and other mutagenic tests are predictive of tumor producing potential. Many of us in toxicology are not impressed with this notion, and more recent data imply that the potentials for such predictions are tenuous, to say the least.

Table 4. RJ-4 (TH-DIMER)

ACUTE TOXICITY

Oral	Mouse	LD Lo = 250 mg/kg
	Rat	LD 50 > 16 g/kg
Intraperitoneal	Rat	LD 50 = 3.2 (2.5 - 4.2) g/kg
4 Hr Inhalation	Rat	LC Lo = 3200 mg/m ³

EFFECTS

Highly Objectionable Odor
Respiratory Tract Irritation
Eye and Skin Irritation Studies in Rabbits - Negative

Table 5. RJ-5 (SHELLDYNE H)

ACUTE TOXICITY

Oral	Rat	LD 50 > 16 g/kg
Intraperitoneal	Rat	LD 50 = 3.0 (1.9 - 4.8) g/kg
4 Hr Inhalation	Rat	LC Lo > 1969 mg/m ³

Table 5 (Continued)

EFFECTS

Highly Objectionable Odor
Respiratory Tract Irritation
Eye and Skin Irritation Studies in Rabbits - Negative

REFERENCES

Burdette, G. W., Jenkins, L. J., Williams, F. W.: Airbreather Fuels
(Status Rpt), China Lake, CA., Nav. Wps. Ctr., 1974
AMRL-TR-76-57, Wright-Patterson AFB, Ohio

Table 6. RJ-4 AND RJ-5 CHRONIC TOXICITY

EXPOSURE PARAMETERS

Exposure Time = 6 Months, 6 Hrs/Da, 5 Da/Wk
Exposure Concentrations: RJ-4 = 2 mg/L (298 ppm) near saturation
RJ-5 = 0.15 mg/L (20 ppm) near saturation
Animals/Exposure: 8 Dogs, 4 Monkeys, 50 Rats, 40 Mice

EFFECTS

RJ-4 and RJ-5	Respiratory Irritation - Monkeys, Dogs, Rats Incidence Bronchitis and Bronchopneumonia in Dogs and Rats
RJ-4	Weight Depression in Dogs and Rats Kidney and Liver Hyperplasia in Rats
RJ-5	Weight Depression in Dogs

ONCOGENIC POTENTIAL

Not Clear-cut
If Oncogenic - Low Potency

MUTAGENIC POTENTIAL - RJ-5 AND RJ-4

Microbial Assay (Ames) - Negative
Mouse Lymphoma Test - Negative
Unscheduled DNA Synthesis - Positive (Risk Minimal)
Dominant Lethal Test (Mouse and Rat) - Negative

REFERENCES

AMRL-TR-76-57, AMRL-TR-78-23, and AMRL-TR-78-45, Wright-Patterson AFB, Ohio

Many false positives and negatives are showing up as such testing proceeds. In this instance the tests were negative; however, Table 7 shows that RJ-5 produced more tumors than either control or RJ-4. Although the numbers of animals are small, these data red flagged the possibility that RJ-5 might be a weak tumor producer. We are in the process of repeating this work with more animals to get statistical validity.

Table 7. TUMOR INCIDENCE IN MICE EXPOSED TO RJ-4 AND RJ-5
FOR SIX MONTHS AND HELD ONE YEAR POSTEXPOSURE

	<u>CONTROL</u>	<u>RJ-4</u>	<u>RJ-5</u>
<u>TUMORS IN MICE DYING</u> <u>DURING POSTEXPOSURE PERIOD</u>			
SARCOMA	2/5	3/6	4/6
ALVEOLARGENIC CARCINOMA	1/5	0/6	0/6
OTHER	0/5	1/6	0/6

<u>TUMORS IN ALL MICE</u>			
LYMPHOSARCOMA	0/17	0/18	2/20
ALVEOLARGENIC CARCINOMA	1/17	0/18	5/20
ALVEOLARGENIC ADENOMA	0/17	2/18	0/20
BRONCHOGENIC CARCINOMA	0/17	0/18	1/20
HEMATOPOIETIC SARCOMA	2/17	2/18	3/20
MYELOSARCOMA	<u>1/17</u>	<u>1/18</u>	<u>1/20</u>
TOTAL	4/17	5/18	12/20

REFERENCES: AMRL-TR-76-57, WRIGHT-PATTERSON AFB, OHIO

The pertinent point is that although the two compounds are close congeners chemically, they both produce effects at vastly different dose levels, and their oncogenic potentials may also be completely different; so much for generic toxicology and for the possibility that short term testing for mutagenic effects is predictive of oncogenic potential. From a scientific management view, neither alone may be trusted completely to give the total answer and use of the short term test did not save time or money. There is no short cut for such work.

Of importance to the USAF is the fact that if RJ-4 or RJ-5 were now modified by opening one carbon-to-carbon bond or adding a methyl group, the process would have to be done all over. This is the point that must be driven home for propulsion engineers and managers. Small changes in chemistry can make vast differences in biological activity, and the gathering of such data takes a long time and is extremely costly. Biological lead time is far greater than that necessary for chemical development. Since most chemical companies are reluctant to spend great

sums of money for toxicology of a developing compound which may have only small military use, it is obvious that DOD must pay the bill if progress is to be made.