TOXICITY TESTING OF ALTERNATIVES: AN INDUSTRY PERSPECTIVE

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This paper addresses the chemical industry's views on the toxicity testing of alternatives. First, it presents an overview of the factors which are considered in designing a typical toxicology program followed by a discussion of the activities of the Program for Alternative Fluorocarbon Toxicity Testing *(PAFT),* a cooperative effort sponsored by the major CFC producers to expedite the development of toxicology data for possible substitute fluorocarbons.

Authors of the book ***What You Need To Know To Live With Chemicals*** (1) remind us that "A swiftly, negative reaction is experienced by many people hearing the word chemical. Chemicals are usually considered to be dangerous materials which are produced by, used by, and disposed of by the chemical industry. Chemicals are blamed for causing cancer, birth defects, environmental pollution, and most of the other ills facing the world today. In short, chemicals are held responsible for the general deterioration of our earth and all its inhabitants." It is not surprising that the public feels this way given the large number of chemicals which have been put in commerce in the not too distant past with little understanding of their effects on health and the environment.

In contrast, the modern chemical industry operates under the mandate to design, manufacture, handle, distribute and dispose of its products safely and without creating unacceptable risks to the population and the environment. This clearly positions toxicology as a basic element of American industry and an integral part of the chemical manufacturer's commitment to insure the safety of its employees, customers and the environment. The current reduction of and the eventual ban of the manufacture and sale of chlorofluorocarbons challenges the chemical industry to develop alternatives that are not only environmentally inert but also share the low degree of toxicity of the current CFCs. Even though the CFCs now in use have been implicated in the depletion of the earth's ozone layer, it should not be forgotten they were developed as safe, economical alternatives to the potentially hazardous refrigerants in general use in the early part of the century. They are non flammable, not corrosive, not explosive and most importantly, of very low toxicity. While we have learned that slight modifications in the structure of these molecules can significantly reduce their potential to react with stratospheric ozone, we also must be aware that

slight changes in structure can also increase their toxicity. We must assure that new alternatives are not only safe to the environment but also to the public.

Toxicity testing is routinely performed on all new chemicals prior to their entering the market, Data obtained from such tests help "weed out" unsafe products during development, supply information for the preparation of labels and material safety data sheets to assure safe handling and use of the chemical, provide guidance for managing spills and emergency releases, allow for the establishment of safe exposure limits, dictate effluent and waste disposal procedures and fulfill regulatory requirements both within and outside of the United States.

A unique testing program is designed for each chemical whether it be a raw material, intermediate, existing or new product. Toxicity testing is usually performed in a tiered structure beginning with acute (short-term) exposure and, if needed, proceeding through tests which address chronic (long-term) exposure. All chemicals undergo acute testing to provide basic infoxmation on the hazards associated with the compound. Such information may also be used for the design of longer-term tests. Many factors need to be considered to determine the type and degree of toxicological tests to be performed on a chemical.

The potential for exposure is of primary concern in designing a testing program. The exposure to a low volume chemical intermediate handled within a controlled industrial setting may be limited to an accidental spill or splash and require only acute tests. In contrast, a chemical which will be released into the environment has the potential to expose a large portion of the population over a long period of time and consequently will require a more extensive toxicology testing program.

Production volume is also a major determinant of a toxicology testing program. The small volume specialty chemical generally requires less testing than a large volume commodity chemical. Exposures are much easier to control and regulate in a small specialty market than when a large portion of the population has access to the chemical, either directly or indirectly. In Europe, the type of tests required is directly linked to the volume of the chemical to be marketed.

Potential routes of exposure as well as likely target organs also need to be considered in determining the type of tests to be conducted. Many chemicals cause different toxic effects depending on the route of entry. Chemicals having the potential to affect specific organ systems such as the central nervous system or heart may require specialized tests.

Other factors considered in designing a testing program are cost, timing and laboratory availability. The cost of a testing program may be prohibitive especially in the case of a product in early stages of research and development where the overall viability of the product is uncertain or where the potential market share for a new chemical is anticipated to be insufficient to cover the required test costs. In the latter case, several producers may agree to share the cost of the testing. In the former case, the testing may need to be conducted in phases, where the longer term and more costly studies are performed during later stages of product development when more information is available as to the potential marketability of the chemical. With this approach money may be saved "up-front," reducing the financial loss if a product does not become a viable candidate for the market. However, there is also an end risk that unexpected toxicology findings in the later studies may prevent a viable chemical from being marketed after a considerable investment has been made in its development.

Timing also plays a critical role in how a testing program is to be conducted. In the case of the CFC alternatives, the proposed ban of existing chemicals in the near future necessitated an accelerated testing program be conducted early in the development of the alternatives. The inability to schedule the toxicology tests to coincide with product development created unique problems. In some cases the supply of test material was insufficient to support the long term tests and the cost of synthesizing the chemicals exceeded the costs of the tests.

Laboratory availability can be a significant factor depending on the type of tests to be conducted. In the case of the CFC alternatives, the number of labs which could conduct long term inhalation studies and other types of specialized tests was limited. It was clear that several alternatives would be under development simultaneously, competing with each other and other types of chemicals for a finite number of laboratories.

A final but important consideration which must enter into the design of a toxicology program, is the potential geographic market for the chemical. Toxicological testing requirements of individual countries often differ both in the type of testing to be conducted and the design of the studies. In order to prevent unnecessary repetition of studies and delays in product registration, the testing program must be harmonized to address the regulatory concerns of all countries involved.

The remaining portion of this paper presents an overview of the Program for Alternative Fluorocarbon Toxicity Testing (PAFT) chaired by Dr. George Rusch of Allied-Signal Inc. PAFT represents an approach by the chemical industry to evaluate the toxicity of alternative fluorocarbons

by pooling resources to overcome many of the obstacles in designing a testing program I have described.

Chlorofluorocarbon producers recognized in 1987 the need to work together to expedite the rapid development of toxicology data for alternative fluorocarbons. The PAFT program is unique in many aspects. It represents the first time that companies around the world from one industry have joined together to evaluate the toxicology of limited products or research chemicals. The PAFT committee is comprised of an international group of companies from Asia, Europe and the United States. Countries represented on the committee include the Netherlands, Japan, France, Germany, United Kingdom, Italy, Belgium, Korea and the United States.

The advantages of the companies working together are numerous and include (1) pooling of existing data, (2) pooling of scientific expertise, (3) conservation of resources, (4) conservation of limited quantities of research grade test chemicals not in commercial production, (5) reduction of the time to obtain results, (6) effective use of limited toxicology testing laboratory space, (7) collaboration on the development of the test data, (8) sharing of results with all member companies and, (9) insurance of rapid publication of results.

The first two chemicals to be evaluated under the PAFT I program were HCFC 123 (1,1-Dichloro-2,2,2-trifluoroethane) and HFC 134A (1,1,1,2-Tetrafluoroethane). Subsequently, under PAFT II and PAFT II, HCFC 141B (1,1-Dichloro-1-fluoroethane) and HCFC 124 (1-Chloro-1,2,2,2-tetrafluoroethane) and HFC 125 (1,1,1, 2,2-pentafluoroethane) are being evaluated, respectively.

The testing program includes: acute exposure toxicity - an assessment of responses obtained from a single high level exposure as would occur during accidental release; genotoxicity - for mutagenic activity and as an early indicator for possible carcinogenic activity; environmental exposure toxicity - an indication of the chemicals potential to affect living organisms in the environment; developmental exposure toxicity studies - which provide information on the potential for the chemical to induce developmental effects (birth defects); subchronic exposure toxicity - to provide an assessment of the overall toxicological action of these new chemicals; reproductive toxicity - to evaluate the potential of the chemical to effect reproductive capability; chronic exposure toxicity and carcinogenicity - studies conducted over the lifetime of the test animals to see if the chemical exposure results in either a late in-life toxicity or an increase incidence of cancer. To date, over 100 individual toxicity tests have been conducted in over 15 laboratories worldwide. With a cost per compound in the range of 3 million to 5 million US dollars, the total commitment of the

PAFT companies to health and safety testing of the new alternatives is already on the order of 25 million US dollars.

The results of the testing available to date indicate that for the alternatives considered, there is nothing to preclude the use of each alternative for the specific purpose for which it is being considered. However, in some cases, exposure limits will need to be set lower than for existing CFCs. For example, the occupational exposure limit for HCFC 123 will be lower than for CFC 11. In addition, it is important to remember that not all testing has been completed at present and additional toxicological findings could add further restrictions on the use of the alternatives.

In summary, the PAFT program represents a far-reaching, balanced approach to the toxicology evaluation of, at present, five of the possible alternative hydrofluorocarbons. The program integrates past and present toxicological information including elements of acute, subchronic, developmental and chronic inhalation toxicity studies, genotoxicity studies, oncogenicity studies and environmental studies. PAFT is attempting to derive the maximum amount of information in a minimum of time and run a cost efficient program that recognizes the current shortages of test compounds, research nature of the programs, and uncertain economic future for the chemicals. The PAFT program seeks, through the development of a broad support base (currently 15 companies from eight countries) to comprehensively evaluate several chemicals to provide industry and the public with safe, viable alternates to current chlorofluorocarbons. As a result of the mutual cooperation, most of the tests in PAFT I and II, excluding the chronic studies, have been Completed and work is currently underway on the PAFT III program.

REFERENCE

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