



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

SEP 3 1982

MEMORANDUM

SUBJECT: Irgasan^(R) DP 300
(Triclosan) Request for Removal of Label Warning:
DO NOT USE FOR BABY DIAPER LAUNDRY

TO: Arturo Castillo (PM-32)
Disinfectant Branch, RD (TS-767)

FROM: *[Signature]* 8/20/82
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Toxicology Branch, HED (TS-769)

THRU: William Butler, Head *WMB*
Review Section III

William Burnam, Deputy Chief
Toxicology Branch

Registrant: Ciba-Geigy Corporation
Ardsley, NY 16502

Compound: Irgasan^(R), DR 300, (Triclosan)
Caswell 186A

100-502

Action

The registrant requests that the label warning statement, DO NOT USE FOR BABY DIAPER LAUNDRY, be removed from fabric softeners containing Irgasan.

Recommendation

Toxicology Branch recommends that the request be denied. Based upon its pesticidal activity, it is not possible to safely use triclosan in contact with the infant.

Background

Irgasan^(R), triclosan, (5-Chloro-2-(2, 4-dichlorophoroxy) phenol, is an antimicrobial agent registered by the EPA for use in the treatment of fabrics

and other uses. EPA registered uses, which can lead to human dermal exposure, include laundry soaps with bacteriostatic action and laundry fabric softeners with bacteriostatic action. When the products are used on cloth, active concentrations of triclosan remain on the fabric. In 1977, the Agency made a preliminary evaluation of the potentially harmful effect of triclosan on infants exposed through treated diapers. As a result of this evaluation, an agreement was made with the registrants of triclosan that the label statement "Do Not Use for Baby Diaper Laundry" be placed on all triclosan-containing products. Subsequently, Ciba-Geigy has submitted toxicology data in order to convince the Agency that triclosan is safe for this use and the label warning is unnecessary. Several Toxicology Branch reviewers have examined the registrant's submissions and indicated ~~some~~ deficiencies in the data available.

The evaluation of triclosan's potential for harm through use on diapers has been complicated by the fact that essentially all of the major toxicity studies were performed by Industrial Biotest Laboratories (IBT) and have required validation.

Despite the toxicology problems, the following critical facts are available:

1. An active residue of triclosan remains on fabrics treated with triclosan-containing products.
2. Triclosan can be extracted with human urine from treated fabrics.
3. Triclosan can penetrate animal and human skin.

Thus, the potential for systemic triclosan toxicity follows washing diapers in triclosan-containing products.

Toxicology Requirements and Available Data

An extensive body of toxicological data is required for registration of a compound which will be used extensively in contact with the human skin. In addition to the acute studies required to evaluate the acute toxicity of the concentrated material, the following subchronic and chronic studies are usually required.

Subchronic oral toxicity (90-days)
Subchronic dermal toxicity (90-days)
Chronic feeding study (2 years)
Oncogenicity study (2 species)
Teratology study (2 species)
Reproduction study (2 generations)
Metabolism Study

An acceptable metabolism study has been received by the Agency; however, the remaining requirements have been the subject of the following IBT studies.

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| <u>IBT #</u> | <u>Study</u> |
|------------------------------|--|
| J4915 | 18-Month Dermal, Mouse |
| 662-0220 and 621-04784 | 90-Day Dermal, Rhesus Monkey |
| 622-04554 | 90-Day Oral, Mouse |
| 622-05278 | 18-Month Oral, Mouse |
| 622-0647 | 2-Year Oral, Rat |
| J7112 and P7113 | Reproduction and Teratology Studies, Rat and Rabbit |

All of the studies except #622-06047, 2-year rat, have been reviewed in the validation process and classified Invalid. These studies cannot be used to satisfy the data requirements. Experience in the IBT review process strongly suggests that the remaining study will also be invalid. Thus, the toxicological data base necessary for the registration of triclosan no longer exists.

Toxicological Considerations For Infant Exposure

In considering the use of triclosan on diapers, it is necessary to determine if the infant presents any unique toxicological concerns which may require special testing or even make safe exposure impossible to obtain.

The human infant is born immature in several critical organ systems of which the Central Nervous System (CNS) is the most important. The human brain continues to grow in size and complexity for several years after birth. Interference with its normal development can produce toxic effects ranging from gross structural abnormalities to subtle but significant behavioral abnormalities and effects on developing "intelligence." In general, the usual toxicological testing, even if performed on newborn monkeys, will show only gross developmental abnormalities, physical and/or behavioral. Considering the importance of the organ and function at risk, special testing is appropriate.

A study involving dosing of newborn primates daily during neurological development, coupled with sensitive physiological and behavioral testing, is indicated to assess safety for the infant.

The immaturity and development of detoxification mechanisms in the infant is another source of concern. This possible source of increased toxicity is more readily amenable to toxicological evaluation. Determination of the

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kinetics of triclosan metabolism and excretion in newborn and young adults in at least two mammalian species should serve to detect any significant deficiencies in the newborn. These differences can be evaluated in light of the biochemistry of the human newborn's detoxifying enzymes.

A third developmental item of concern pertains directly to the pesticidal activity of triclosan. The fact that triclosan is to be used for its antimicrobial effects at effective doses makes it in fact the major item of concern. The infant is born essentially sterile and begins to acquire its normal skin (and intestinal) flora at birth. At this time, the immunological system is immature. Exposurance with anoxic (germ-free) animals has provided convincing evidence that the acquiring of normal flora and maturing of the immunological system must occur in parallel. Without this timely colonization the immunological system will not develop properly leading to immunological problems throughout the individual's life span. Triclosan has been shown to be effective against many of the normal flora of the human skin and intestine. Also of particular importance is the fact that *Pseudomonas aureginosa* is quite resistant to triclosan, so that use of triclosan can lead to infection by this potentially life-threatening organism.

Thus the very fact that triclosan is effective against normal skin flora is potentially harmful to the individual exposed. The potential for harm even extends to the normal adult, where exposure to effective doses of triclosan may so alter the normal skin flora as to allow overgrowth by abnormal strains or foreign species.

Ciba-Geigy Data Submission, Jan. 20, 1982

In their submission of January 20, 1982, Ciba-Geigy submitted 42 reports on the contaminants of triclosan,

[REDACTED] These compounds are present in technical triclosan at concentrations of [REDACTED]

The reports were examined but not reviewed in detail because the primary agency concern is with the toxicology of triclosan and its deficient data base. However, the following general observations can be made about the submission:

1. The compounds appear biologically inert by the oral route.
2. The dermal studies are in German and the xerox copies are so poor as to make them impossible to read.
3. The teratogenicity reports are incomplete, lacking data on number of animals, number of litters, number of pups per litter, etc. The first three compounds were inactive at 3000 mg/kg/day, the fourth compound was embryo lethal at 1000 and 3000 mg/kg/day but not teratogenic.

MANUFACTURING PROCESS INFO. NOT INCLUDED

4. The mutagenicity tests reported were uniformly negative.

Considering the high doses given orally to mouse and rat (up to 15 gm/kg) and the variety of mutagenicity tests performed on each compound, it appears likely that these compounds are biologically inert.

Conclusions

1. Label warning against uses on diapers.

Toxicology Branch recommends that triclosan not be used on diapers and on cloth in direct contact with the infant. The major concern is with the antibacterial effect which can interfere with the normal flora of the skin and select for potentially harmful species. A quantity of triclosan sufficient to be effective for its antibacterial propose is potentially harmful if it accomplishes that purpose. From this we conclude that there are no conditions under which triclosan can be safely used in contact with the infant skin.

2. Data gaps produced by the invalid IBT studies.

In order to maintain the triclosan registration, the following studies must be performed to replace the invalid IBT studies.

1. Subchronic dermal toxicity, 90-days
2. Chronic feeding or dermal study, 2-years
3. Oncogenicity dermal or ~~dermal~~^{oral}, 2-species
4. Teratogenicity studies, 2-species
5. Reproduction study

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