UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

June 6, 2001

MEMORANDUM

Subject: Consideration of Low Volume Eye Test in Support of Four Product Registrations

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BACKGROUND

Antimicrobials Division (AD) has received data from The Procter and Gamble Company (P&G) in support of the use of the Low Volume Eye Test (LVET) as an alternative test for eye irritancy as related to four specific products. These products are Z-1 (EPA File Symbol 3573-AO), Mariner (EPA Registration No. 3573-72), FIT Fruit & Vegetable Wash (EPA File Symbol 3573-TR), and Scrubbing Wonder Automatic Dishwashing Detergent (EPA File Symbol

3573-AI). An LVET study report was submitted for each, along with summaries of consumer incident data for closely related non-'pesticidal' products which have a post-market history. More recently, on 02/16/01, P&G submitted further information to show general consistency between LVET results, Draize results, consumer incident data and, in some cases, human volunteer studies. At the request of Antimicrobials Division, P&G has listed these results according to types of formulations and chemicals and has also given information on the composition of many of the formulations.

RECOMMENDATION

P&G has proposed the LVET test as an alternative to the standard Draize eye test. P&G claims that the LVET is more relevant to real world exposures (i.e., the volume of exposure in the LVET [10µl] is more realistic than the 100µl exposure in the traditional test). P&G also claims that the use of the rabbit is inherently conservative due to the relative sensitivity of the rabbit eye vs. the human eye. P&G also notes that the volume capacity of the human conjunctival sac is significantly less than that of the rabbit. P&G further claims that the extensive consumer incident database that they have accumulated for the above four products shows a close correlation with results of LVET testing. P&G has provided a comparison of results of traditional Draize testing with those of LVET testing for various types of products, incorporating many of the ingredients that make up the above four products. This comparison of results (a chart document submitted on 02/16/01, herein referred to as "P&G Results Comparison") shows that the LVET test and the traditional Draize test tend to give comparable results for purposes of eye irritancy classification.

AD considers that a weight of the evidence approach is appropriate for supporting the use of the LVET on behalf of the four products named above. In this light, AD recognizes that the rabbit eye is inherently more sensitive to chemical insult than the human eye (with some exceptions) and thus generally provides a level of conservatism in classifying chemicals for eye irritancy. AD also recognizes that P&G has provided a substantial amount of evidence in support of the lack of significant human ocular injuries to these four products from accidental exposures, and that the results of LVET testing strengthen this evidence. P&G has also agreed to employ Toxicity Category III labeling language for at least two of these products even though LVET test results place them in Category IV.

Note that the LVET is not a guideline study, and the Agency does not consider it sufficient by itself to satisfy the eye irritation data requirement for pesticides. However, as indicated below, AD has decided to consider the use of LVET studies on a case-by-case basis, where supplemented by substantial supporting data.

The Office of Pesticide Programs still considers the Draize test as the acceptable test methodology for eye irritancy and has not yet formally adopted an alternative test.. However, in light of the information presented in support of the four antimicrobial products mentioned above, AD will accept the results of LVET testing for the Z-1, Mariner, FIT, and Scrubbing Wonder

products. It is emphasized that the LVET results are in support of these four products only and that this memorandum does not constitute a policy decision by AD or the Agency in support of the wholesale use of LVET testing for eye irritancy. Any other chemicals or products would require separate submissions and supporting data.

AD has reviewed the submitted eye irritation data support for the four P&G products identified above, and resulting comments for each product are noted below. These are followed, at the end of the memorandum, by several comments on product labeling.

Note that, since the information in the above paragraphs have general applicability, they are not repeated below for each product.

Z-1 (EPA File Symbol 3573-AO)

With the exception of didecyl dimethyl ammonium chloride (DDAC), the other ingredients in Z-1 are not of notable concern with respect to eye irritation at the concentrations present. This viewpoint is strengthened by P&G's summary of consumer incident data for certain formulations that are similar to Z-1 except that they do not contain DDAC. Moreover, the LVET study conducted on one of these formulations showed results of a non-irritating nature. This particular formulation's characteristics seem to fit in well – in the above-referenced P&G Results Comparison chart – with those listed Hydroalcoholic formulations that showed reasonable consistency in test results between the LVET and Draize methods.

As for the ingredient DDAC, note that P&G's Results Comparison cites Draize test results that indicate Category III for 3% dimethyl ditallow ammonium chloride (which is similar to DDAC in that both are aliphatic quaternary ammonium compounds) and Category IV for 0.1% benzalkonium chloride (another quaternary ammonium compound). Also cited for these substances were LVET results indicating Category IV. These Draize and LVET results support the expectation that the addition of the DDAC at 0.14% of the Z-1 formulation does not present more than a moderate eye irritation hazard.

Consequently, AD recommends for the Z-1 product assignment of eye irritation Toxicity Category III.

The outcome of the P&G consumer incident data for Z-1 is summarized in P&G's 02/16/01 submission regarding Z-1, which indicated that 100% of the reported cases of eye irritation from exposure to the product cleared within 48 hours, consistent with the above classification.

Mariner (EPA Registration No. 3573-72)

The submitted eye irritation information appears sufficient in support of Mariner. The innocuous nature of the LVET results for Mariner is supplemented by the fact that the Mariner formulation would appear to be at worst no more acutely irritating to the eye than two other P&G formulations that were previously assigned to eye irritation Toxicity Category III. They are Comet Bathroom Spray, (EPA Registration No. 3573-54); and Mr. Clean Bathroom Liquid,

(EPA Registration No. 3573-53). In comparing Mariner to those two products, a concern which may arise – regarding a lack of available eye irritation information on a chemical in Mariner that is not present in those products – is allayed by the Draize and LVET study results which are cited for related chemicals by the above-referenced P&G Results Comparison document.

Since Mariner has received its product registration, no further recommendation is necessary. It is noted, however, that the data submitted appear sufficient for the assignment of an eye irritation Toxicity Category III.

FIT Fruit & Vegetable Wash (EPA File Symbol 3573-TR)

[redacted]

Pending registration information may be entitled to confidential treatment

Pending registration information may be entitled to confidential treatment

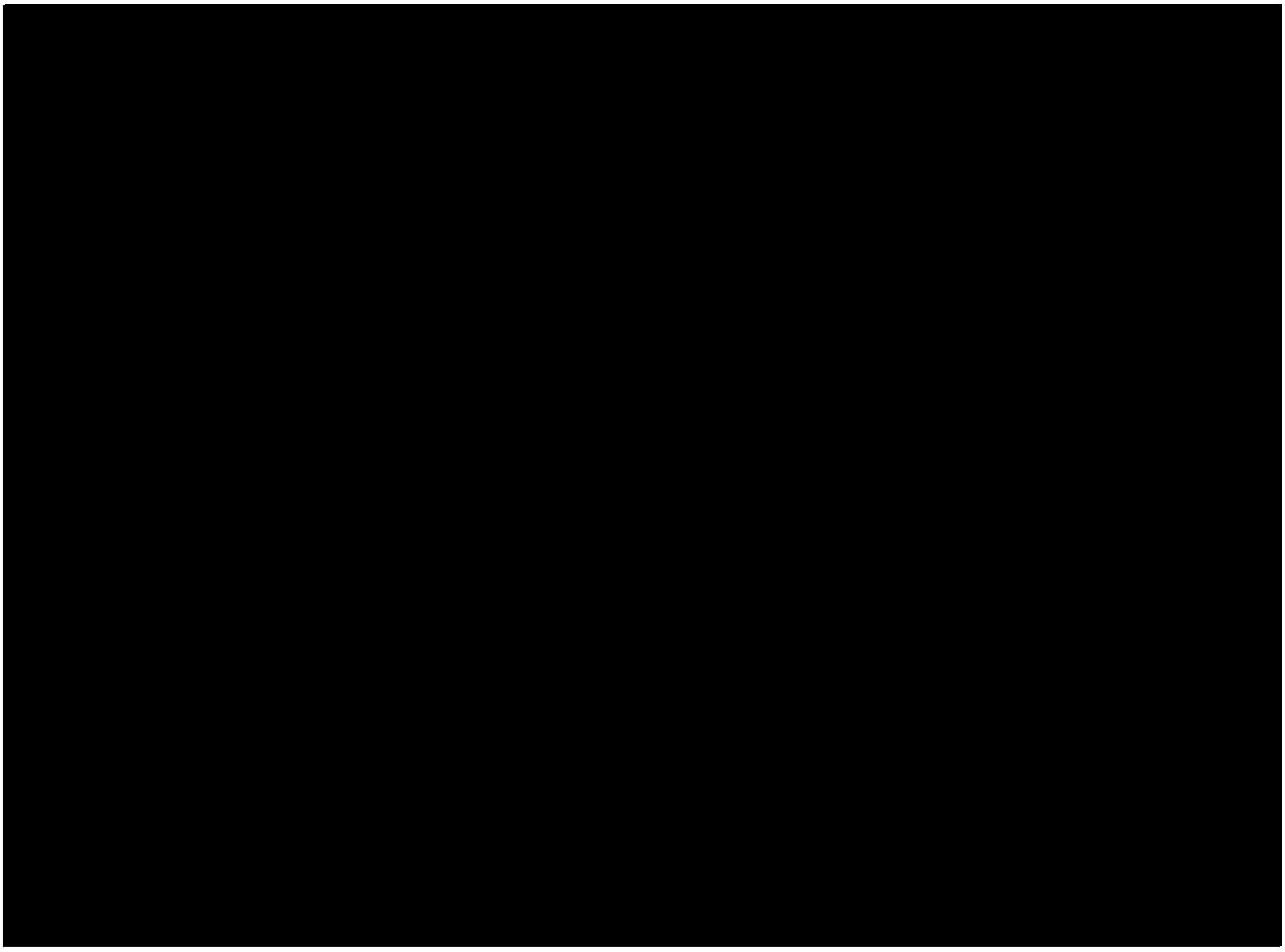
[redacted]

Scrubbing Wonder Automatic Dishwashing Detergent (EPA File Symbol 3573-AI)

[redacted]

Pending registration information may be entitled to confidential treatment

Inert ingredient information may be entitled to confidential treatment



Product Labeling

The human-hazard precautionary statements normally required under the agency's *Label Review Manual* for eye irritation Category III products are as follows: "Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling." P&G has proposed, for at least one of the four products discussed in this memorandum, a shorter set of statements somewhat similar to the following: "Causes eye irritation. Avoid contact with eyes." This shorter set of statements was accepted by the agency in 1998 for P&G's EPA Registration No. 3573-53, and in 1997 for Reg. No. 3573-54. These label statements appear sufficient for adequate protection, in which case it seems reasonable to follow the precedent of accepting them for the products above that are assigned to eye irritation Category III. Agency acceptance of applicant-proposed variations to this already-reduced set of statements is not viewed as likely; but they will nevertheless be reviewed, on a case by case basis.

Precautionary statements for Scrubbing Wonder (EPA File Symbol 3573-AI), for which eye irritation Category II is recommended above, will be addressed by Product Science Branch in a separate memorandum.

Note that the First Aid statements on the product labels will need to comply with PR Notice 2001-1 (available on the Internet at *http://www.epa.gov/PR_Notices*), which supersedes the guidance for First Aid statements in the *Label Review Manual*.

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