UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

Subject: D274170
Tide With Bleach Opal, EPA File Symbol 3573-TG

From: Wallace Powell, Biologist
Product Science Branch
Antimicrobials Division (7510C)

07-25-01

Thru: Karen P. Hicks, Team Leader
Chemistry/Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

7/25/01

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510C)

To: Marshall Swindell, Product Manager, Team 33
Karen Leavy-Munk, Team Reviewer, Team 33
Regulatory Management Branch I
Antimicrobials Division (7510C)

BACKGROUND

The applicant, The Procter & Gamble Company (P&G), has submitted a package for registration of the subject product, Tide With Bleach Opal. The package includes the following Guideline studies in support of product-specific acute toxicity data requirements:

Acute Oral Toxicity	Submitted study, MRID 453686-05
Acute Inhalation Toxicity	Submitted study, MRID 453686-07
Acute Dermal Toxicity	Submitted study, MRID 453686-06
Skin Irritation in Rabbits	Submitted study, MRID 453686-09
Skin Sensitization	Submitted study, MRID 453686-10

For acute dermal toxicity, P&G has also referenced other data (Non-Guideline) in order to support a different acute Toxicity Category than the one indicated by the above-listed study. For the eye irritation data requirement, P&G has submitted a Low Volume Eye Test (LVET) in rabbits, MRID 453686-08. For skin irritation, P&G

has submitted a skin irritation test in humans, MRID 453686-11, in order to support a different acute Toxicity Category than the one indicated by the above-listed study.

The seven studies cited above which received MRID Numbers were initially reviewed for Product Science Branch (PSB) by Oak Ridge National Laboratory. The reviews are attached to this memorandum. Any PSB disagreement with the reviews appears below; the reviews themselves have not been edited by PSB.

The subject product, Tide with Bleach Opal, is labeled as a laundry sanitizer, with the active ingredients sodium nonanoyloxybenzenesulfonate (NOBS, EPA code 089053) at 5.28% of the formulation by weight, and hydrogen peroxide (EPA code 000595) at 1.61% by weight.

RECOMMENDATION

Acute oral toxicity

The submitted study is acceptable in support of acute oral Toxicity Category III.

Acute inhalation toxicity

The submitted study is acceptable in support of acute inhalation Toxicity Category IV.

Acute dermal toxicity

The submitted Guideline study is acceptable in support of acute dermal Toxicity Category III. However, P&G has submitted further information in order to support a different Category.

(a) The case for assigning Category IV or waiving the Category III label statements:

In regard to assigning Category IV, P&G has appealed to precedent: For EPA Reg. No. 3573-56, the agency apparently assigned Category IV (or waived label statements regarding acute dermal toxicity), even though Category III was assigned in a PSB review based on a submitted study, MRID 442734-07. (The case was a bit different then for Reg. No. 3573-56 than it is now for the subject product because, in addition to a 2000 mg/kg LD_{50} lower limit, the Reg. No. 3573-56 study indicated a 5000 mg/kg upper limit. This difference in the two cases, however, does not detract from P&G's appeal to precedent for the subject product.) Presumably the reason that Category III label statements were not required in the case of Reg. No. 3573-56 is that – as P&G states – summaries of supplemental data were submitted, including the following:

> "...summaries of subchronic dermal toxicity data on Tide with Bleach, a prospective clinical study evaluating use of a 60% paste for hand laundering, and a summary of human skin effects reported via a 1-800 number which is

on the label of all our products. These data are consistent with the results of the acute dermal toxicity study on Tide with Bleach Opal and demonstrate no evidence of systemic toxicity or adverse effects, even at the limit dose of 2,000 mg/kg."

It may also be noted that the agency's Reregistration Eligibility Decision (RED) document for Peroxy Compounds cites a dermal LD_{50} of 4060 mg/kg for hydrogen peroxide. This might lend support to the idea that the 1.6% hydrogen peroxide activator in the subject product is not likely to add more to the acute dermal hazard for this product than would the 5.3% sodium perborate for the Reg. No 3573-56 product.

(b) The case for assigning Category III and requiring the associated label statements:

In regard to the Category III limit dose of 2000 mg/kg, P&G has appealed to international use of this as the highest normally employed limit dose. P&G has also appealed to the 870-1200 Guideline for acute dermal toxicity testing. These appeals are not acceptable in and of themselves. It is true that this Guideline indicates that, where a 2000 mg/kg limit test is successful, precautionary statements "may" still be required, thereby implying that a waiver of such statements on a case by case basis may be possible. However, the 870-1200 Guideline also confirms the policy of normally requiring Category III precautionary statements in such cases, a policy stated in the agency's *Label Review Manual* without mention of any avenue for exceptions.

If P&G means to compare the subject product with the Reg. No. 3573-56 product, PSB does not view the two formulations as being sufficiently similar. PSB finds it difficult to compare expected effects of 1.6% hydrogen peroxide (contained in the subject product) versus 5.3% sodium perborate (contained in the Reg. No. 3573-56 product). The irritation effects of dilute sodium perborate itself are difficult to glean from the literature. Therefore, the similarity of P&G's two products to each other is questionable. And the use of the Reg. No. 3573-56 product as an equal or worse-case point of comparison for the subject product is questionable. (If more information were available for a 5.3% concentration of sodium perborate, it may be helpful.) Although it does seem that the 'inert' ingredient composition of the Reg. No. 3573-56 reference product is likely to be less hazardous than that of the subject product, PSB is moderately concerned about the fact that there are so may differences between the two products. Clinical effects of exposure to a highly formulated product may well vary according to the actions of several ingredients acting in combination. Such combined effects are, of course, unknown to PSB.

Because PSB holds the similarity of the two products in question, the usefulness of most of the surrogate data cited in the above quotation from P&G is quite limited. Only the cited skin irritation study in human volunteers was actually conducted on a version of the subject product. (This is the same as the submitted study in human volunteers, MRID 453686-11; a review of it is attached to this memorandum.)

Skin irritation

The submitted skin irritation study in the rabbit is acceptable in support of Category I. This is PSB's conclusion, although both P&G and the author of the attached study review interpreted the result as indicating Category II. PSB overrides the Category assignment in the attached review. (This statement will serve to amend the record; the review has not been edited by PSB.) Irritation was quite severe at its worst, in all three test animals. Significant other dermal effects were also observed in each animal. The fact that the irritation and other effects were reversible by 21 days does not take the classification out of Category I.

Regardless of the Category, however, Category I does not appear to be a realistic assessment of the hazard to *humans*, in light of much of the other information cited by P&G. Such information includes – as indicated above in reference to acute dermal toxicity – a prospective clinical study evaluating use of a 60% paste for hand laundering, and a summary of human skin effects reported via a 1-800 number which is on the labels of P&G's laundry bleach products. These data are noteworthy. And the Reg. No. 3573-56 formulation (or one closely representing it) for which the data were collected does have its similarities to the subject product (in spite of the above remarks as to limited similarity), since it is a closely related type of laundry bleach product.

In regard to the above-mentioned "prospective clinical study," PSB would like to see the comments from the Moroccan participants. It is assumable based on the study plan that they were the only ones to observe exposed hands on a frequent basis.

P&G has requested a Category IV classification for skin irritation. This is not acceptable. If P&G appeals to precedent, note that what occurred in the past for Reg. No. 3573-56 is that a submitted skin irritation study indicated Category III, but the Category III skin-irritation label statements were not required. This was only a 'jump' from Category III to IV. What P&G is requesting for the subject product is a jump from Category I or II (depending on who is interpreting the submitted Guideline study) to a Category IV. This is a greater leap. A Category II or possibly III assignment would be more recommendable.

The comments regarding limited similarity of formulations (Reg. No. 3573-56 versus subject product) – in the second-to-last paragraph of the "Acute dermal toxicity" section above – can also be said in reference to skin irritation.

The MRID 453686-11 study using human volunteers cannot be compared with a Guideline study, because the dose quantities and instances were very different from those of a Guideline study. As to the fact that humans were used, the agency generally views the use of human volunteer studies as ethically controversial. However, a study like this (in consideration of its outcome and its topical dosing) is not likely to be viewed too critically in that regard.

Skin sensitization

The submitted study is acceptable in support of classification as a Non-sensitizer.

Eye irritation

The submitted study, MRID 453686-08, is a Low Volume Eye Test (LVET). If the study were evaluated as if it were a Guideline study (a Draize study), then, according to the agency's criteria, the result would be eye irritation Category III. PSB considers the submitted study to be acceptable as a Non-Guideline study only. As explained below, it is now PSB's policy to take a weight of the evidence approach to the situation by considering individual LVET studies for possible acceptance on a case by case basis if they are significantly supplemented by further, confirmatory information.

In the present case, that confirmatory further information is not sufficient. In the case of the applicant's four applications for registration for which P&G's LVET submissions have been viewed favorably, summaries of post-market consumer incident data were submitted as specifically related to eye effects. (A good example is Scrubbing Wonder Automatic Dishwashing Detergent, EPA File Symbol 3573-AI. The data summaries submitted are further summarized in a PSB memorandum dated 07/31/00, Data Package D265530.) Submittal of those incident data served to help allay agency concerns about real-world eye irritation hazard – and to help demonstrate consistency between human incident reactions and reactions to dosing in the LVET (in the rabbit), as specifically relating to the product in question (and/or closely related products). Granted, it is helpful that support is lent to the LVET in general by the incident data that has been collected for a variety of P&G formulations, since they have generally yielded outcomes consistent with LVET results. However, to support a specific LVET review on a case by case basis, adequate supplemental confirmatory information on eye irritation, specific to the product at hand, should be provided.

Once the eye irritation data requirement for the subject product has been met, then an eye irritation Toxicity Category will need to be assigned. Because the subject product has proven severely irritating under the conditions of the submitted skin irritation test in rabbits – and because LVET's have been known to occasionally grossly over-represent Draize results when Draize vs. LVET results were compared for various bleach or surfactant products – it would be reasonable to apply a margin of error by placing the subject product in eye irritation Category II. P&G requested Category III. Administratively, precedent *might* dictate that Category III be assigned, if the applicant can argue why this is an analogous situation to that of EPA Reg. No. 3573-56.

Recent regulatory background regarding the LVET:

The LVET is not a Guideline study type and cannot be accepted without adequate supporting information. In order to support consideration of individual submitted LVET's for possible acceptance, P&G previously submitted summaries of consumer incident data for various products. More recently, in a 10/09/00 meeting with P&G, Antimicrobials Division (AD) requested further information to supplement the data summaries already submitted. On 02/16/01, P&G provided such information, in order to support the acceptance – as determined on a case by case basis – of individual LVET studies, each one submitted as an integral part of acceptable eye

irritation data support for an individual product registration. The information in the 02/16/01 submission is meant to show general consistency – for a variety of product types – between LVET results, Draize test results, consumer incident data and, in some cases, human volunteer studies. At the request of Antimicrobials Division, P&G also grouped these results according to types of formulations and chemicals and also provided information on the composition of many of the formulations.

In an internal memorandum dated 06/06/01 (Powell and McMahon to Noble, Brennis, and Heyward: "Consideration of Low Volume Eye Test in Support of Four Product Registrations"), AD determined that information provided by P&G was sufficient to support the acceptance of certain submitted LVET studies for four of P&G's products. (Note that the 06/06/01 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.) Refer to the 06/06/01 memorandum for AD's general rationale for deciding to review and consider LVET studies for acceptability in conjunction with other supporting data and in a case by case manner. However, please note that the 06/06/01 memorandum contains confidential product information and must be handled accordingly.

One of the purposes for P&G's 02/16/01 submitted document was to show that LVET results tend to be consistent with Draize results across a broad range of formulation types. For roughly 87 percent of the 91 tested substances in the document, the LVET and Draize eye irritation Toxicity Categories were either the same or differed by one Category level. In about two-thirds of these 87 percent, the Categories were the same.

Product Labeling

After the eye irritation data requirement has been met – and after the Toxicity Categories for acute dermal toxicity, skin irritation, and eye irritation have been decided by the Product Manager – then a complete set of precautionary (human hazard) and first-aid statements for the product label can be determined.