SDA Fragrance Subcommittee* Report: Industry Surveys Fragrance Sensitization Test Data

By R. J. Steltenkamp (Colgate-Palmolive), K. A. Booman (SDA), J. Dorsky (Givaudan), K. Kohrman (Procter & Gamble), A. S. Rothenstein (Lever Brothers), E. A. Schwoeppe (Procter & Gamble), R. I. Sedlak (SDA), and G. R. Thompson (IFF)

The Fragrance Raw Material Subcommittee of the Soap and Detergent Association (SDA) was formed in early 1977 to review information on the human skin sensitization potential of some fragrance ingredients important to the soap and detergent industry. The committee includes representatives of member companies and fragrance suppliers.

Perfumed products of the soap and detergent industry have had a long history of broad use and a good safety record. Nevertheless, there have been clinical reports of dermatitic patients showing sensitization to fragrance ingredients commonly used in consumer products. Also, several important fragrance ingredients have been reported to have the potential to induce human sensitization. These reports are based on the results of patch tests conducted at abnormally high concentrations under exaggerated exposure conditions. Companies conduct human skin sensitization tests to determine the acceptability of a new formulation prior to marketing. Consequently, a wealth of safety data exists on experimental and marketed products containing fragrance ingredients, fragrance blends used in consumer products, and neat materials from patch tests conducted at test concentrations representing actual consumer exposure concentrations, as well as at higher concentrations. Under the auspices of SDA, skin sensitization data on several important fragrance raw materials were collected and evaluated.

*Fragrance Raw Material Subcommittee of the Biomedical Research Committee of the Soap and Detergent Association.

Information regarding both the extent of existing sensitization in the consumer population and the potential of the material as used in the products of this industry to induce new cases of human hypersensitivity was sought through the surveys. The extent of existing sensitivity in the consumer population may be assessed by the frequency and severity of elicited reactions (pre-existing sensitizations) in a test population to early patches in a patch test sequence. Diagnostic patch testing of dermatitic patients is the major source of elicited reactions reported in the literature. The potential for a material to induce reactions is generally determined from repeated patch tests on normal subjects using exaggerated test conditions.

The surveyed materials are commercially important fragrance materials for which data suggesting a potential for sensitization have been reported. The materials first surveyed were hydroxycitronellal, citral, and cinnamic alcohol. The data gathered on all three have been published.[1-3] The data were also presented to the Joint Advisory Committee of the International Fragrance Association (IFRA) and the Research Institute of Fragrance Materials (RIFM) and to the RIFM Expert Panel. The specific details of these surveys, the data gathered, and conclusions are contained in the separate publications. A summary of this work and overall conclusions are provided here.

Experimental procedure

Data from patch tests conducted in the United States on human subjects were obtained from member companies of SDA and from perfume

suppliers. It was recognized that the details of individual tests in the survey would vary. To assist in the compilation and correlation of data, forms were provided that specifically requested the following common experimental information for each panel of subjects on which data were reported.

Test material

The test material containing the fragrance ingredient was to be identified as belonging to one of four general categories. Product names or trade names, if any, were not to be reported.

The four categories included

- Household products—products having only incidental contact with the skin, such as detergents, cleansers, laundry aids, bleaches.
- Personal care products—products that are intended to be applied directly to the skin, such as soaps, creams, shampoos, talc, perfumes, colognes.
- Fragrance blend—concentrated fragrance mixtures that are used to perfume consumer products; consumers are exposed to the blends only at the low concentrations used in consumer products.

For the fragrance ingredient itself, the following information was compiled.

- Concentration (%) fragrance ingredient in test material.
- Concentration (%) fragrance ingredient in patch test application.
- Patch test vehicle.
- Test method used.
- Number of individual patch tests. (An individual patch test is defined as the test procedure each subject undergoes in which a series of induction patch applications are followed by a single or a series of challenge applications. For example, a single human repeat insult patch test (HRIPT) involved a nine-application induction period in which patches are applied on Monday, Wednesday, and Friday for three weeks. Challenge patches are applied two weeks after the last patch of the induction phase.)
- Number of sensitization reactions. This includes allergic reactions due to pre-existing sensitization ("elicited reactions") or newly acquired sensitivity ("induced reactions").

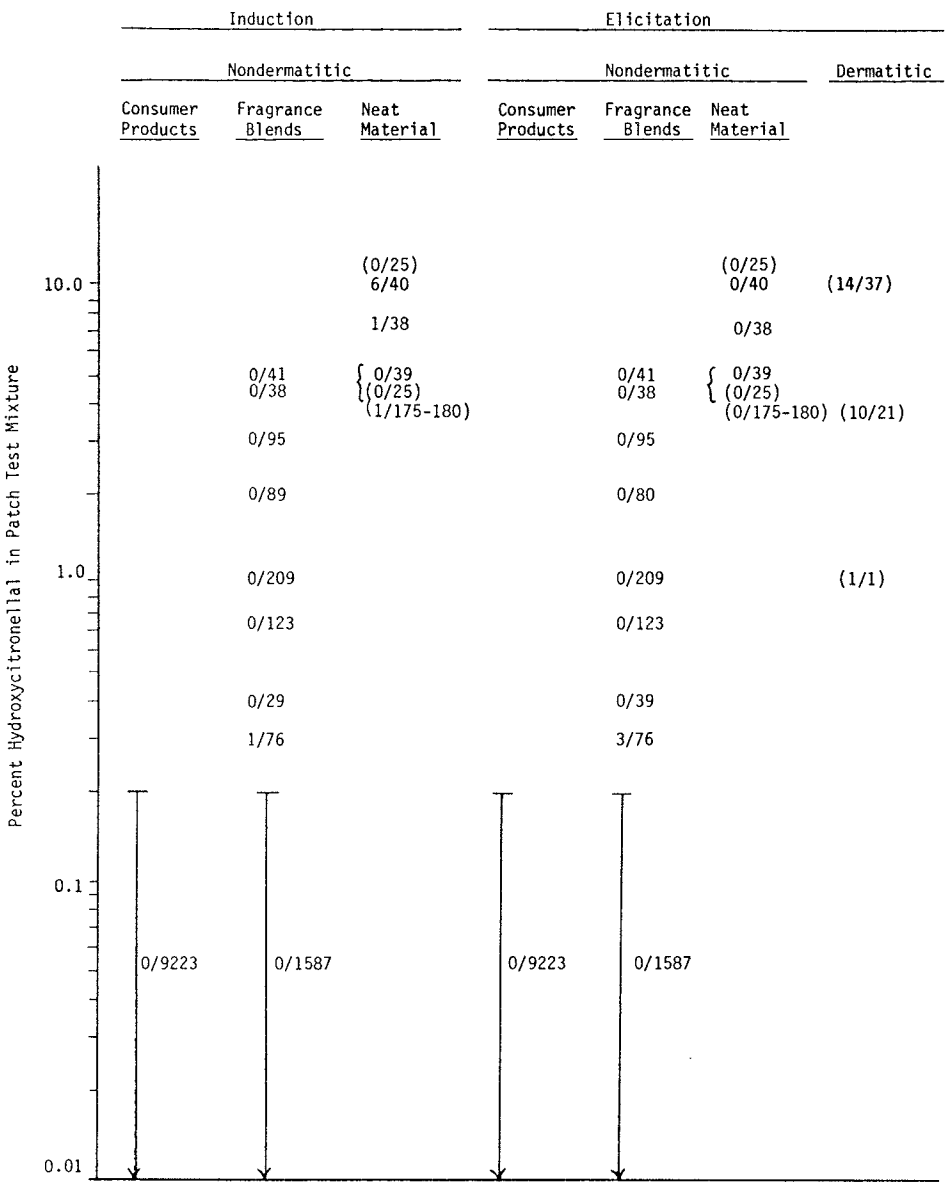
All of the reported tests used the repeated insult patch or prophetic patch test procedures. These techniques are used to assess the potential for a material to induce allergic contact sensitivity, and subsequently to elicit sensitization reactions and have historically represented the most common and widely used methods.[4,5] Both procedures incorporate exposure conditions that exaggerate the sensitization response of the test populations. The patch test methods reported in the surveys involved occluded patches repetitively placed on the same site, multiple patches applied simultaneously, regular exposure for three consecutive weeks, and the use of the pure ingredient or concentrated blends. Typical consumer use patterns for the types of products reported in the surveys generally result in far less exposure. Consumer products are typically used at lower concentrations and in many cases intermittently and for short durations.

The subjects in the tests were volunteers. For availability reasons most were white, female homemakers between the ages of 18 and 65. Subjects were interviewed regarding their history of allergies and this information was reviewed before including them in test panels. Volunteers were excluded from a panel if they were under treatment for skin disease at the time of testing, but were generally not excluded if they only reported the previous occurrence of skin allergies.

Table I

Fragrance Raw Material	Number of Individual Patch Tests	Number of Different Formulations	Range of Exposure Concentrations
Hydroxycitronellal	11,638	127	3×10^{-8} to 10%
Citral	13,014	127	1×10^{-8} to 5%
Cinnamic alcohol	16,530	119	9×10^{-8} to 6%

TABLE II. Hydroxycitronellal: A Summary of Patch-Test Data on Human Induced and Elicited Sensitization



( ) denotes non-SDA data. For details and references see hydroxycitronellal publication, reference 1.

Survey results

The surveys of these three materials provided extensive data revealing that a large number of tests had been performed involving many formulations and a wide range of concentrations (see Table I).

The patch-test data reported in the surveys, as well as patch-test data reported in the literature, are summarized in Table II (hydroxycitronellal), Table III (citral), and Table IV (cinnamic alcohol.) The data are categorized in these tables according to the predictive patch tests done with normal (nondermatitic) subjects to determine the potential for inducing hypersensitivity and the elicited reactions observed with both normal and dermatitic patients. The patch-test data reported in the literature on elicited reactions were primarily obtained from diagnostic patch testing of dermatitic patients. The number of individual patch tests performed along with the number of reactions are listed according to the percent of the test material in the patch-test mixture.

Survey conclusions

Hydroxycitronellal

Exposures to hydroxycitronellal in consumer prod-

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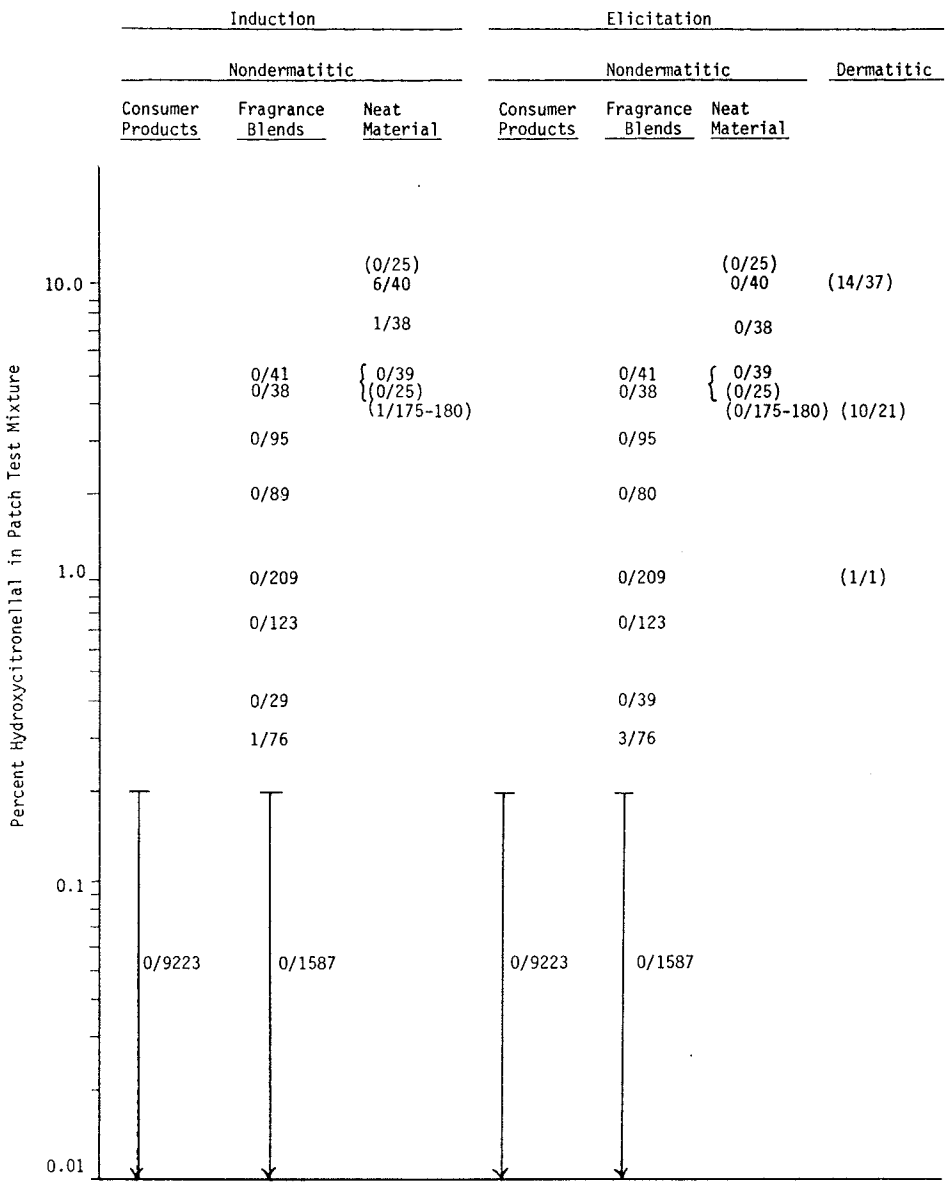

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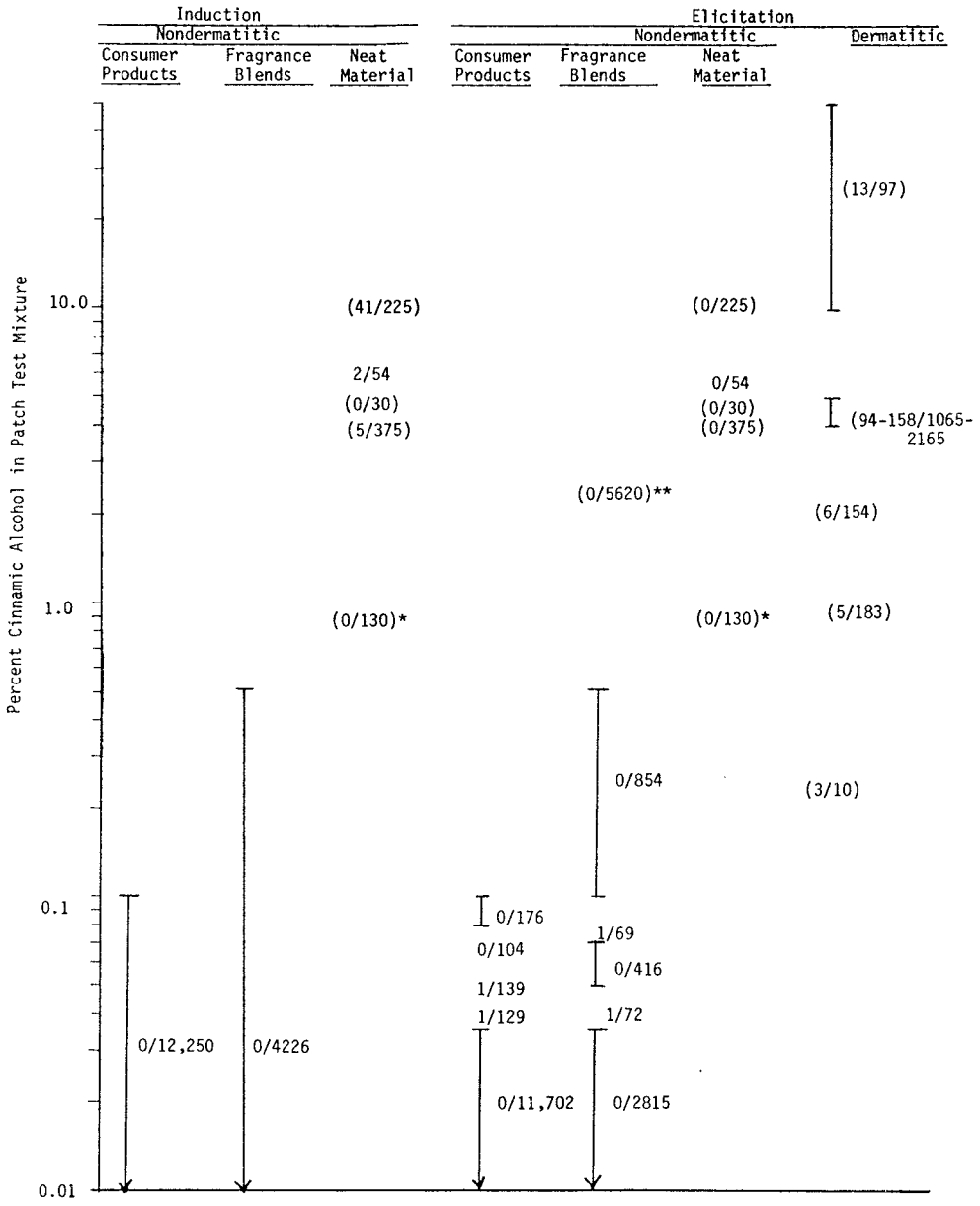
TABLE IV. Cinnamic Alcohol: A Summary of Patch Test Data on Human Induced and Elicited Sensitization



( ) denotes non-SDA data. For details and references see cinnamic alcohol publication, reference 3.
* Subjects were approximately 60% nondermatitic and 40% dermatitic patients. The mean patch-test concentration was 0.87%, maximum 3.2%.
**Subjects were approximately 70% nondermatitic and 30% dermatitic patients. The mean patch-test concentration was 2.5%, maximum 13.5%.

vey at similarly high concentrations indicates that contact dermatitic patients may represent a unique segment of the population.

Citral

Exposures to citral in consumer products did not induce hypersensitivity or elicit sensitization reactions in 10,660 patch tests (Table III). The potential to induce hypersensitivity was observed with the material alone and was concentration-dependent. No induced reactions occurred at the concentration of 0.5% citral in 82 test subjects, whereas induced reactions were observed at 1% to 5% citral. No elicited reactions to citral occurred in any of the 13,014 patch tests reported in the survey nor have any been reported in the clinical literature.

Cinnamic alcohol

Exposure to cinnamic alcohol in consumer products did not induce hypersensitivity in 12,250 patch tests

(Table IV). SDA survey data compared with other available data[7,8] indicate that induction of hypersensitivity to cinnamic alcohol is concentration-dependent. The lowest concentration of cinnamic alcohol that has been tested and reported as inducing hypersensitivity is 4%.[7] Data available from the SDA survey ($\leq 0.4\%$) and a European survey by IFRA ($\leq 3.2\%$)[8] revealed no induced hypersensitivity. Cinnamic alcohol has a very low potential to elicit sensitization reactions (pre-existing sensitizations) at the concentrations used in consumer products, as evidenced by two elicited reactions 12,250 patch in patch tests on consumer product formulations and two elicited reactions in 4,266 patch tests on fragrance blends containing cinnamic alcohol. The high incidence of reactions to cinnamic alcohol in diagnostic patch tests on dermatitic patients and the low incidence of elicited reactions reported in the SDA survey is further evidence that patch-test data obtained from dermatitic patients do not predict the sensitization potential of a material for the normal population.

Overall conclusions

The patch-test data presented on hydroxycitronellal, citral, and cinnamic alcohol provide valuable guidance for their safe use in consumer products. Even though each of these materials has the potential to induce hypersensitivity at high concentrations under exaggerated test conditions, the potential to induce hypersensitivity when tested in consumer products is very low. The induction of hypersensitivity by each material is clearly concentration-dependent. Also, this data indicate that the extent of pre-existing sensitization in the consumer population to the three materials is very low.

References

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