RE-REVIEW

Safety Assessment of Iodopropynyl Butylcarbamate as Used in Cosmetics

Status:	Re-Review for Panel Review
Release Date:	August 16, 2013
Panel Meeting Date:	September 9-10, 2013

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A Hill, Ph.D. James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

1101 17TH STREET, NW, SUITE 412 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: August 16, 2013
Subject: Re-review Document on Iodopropynyl Butylcarbamate

At the June 3-4, 1996 Expert Panel meeting, the Panel issued a final report on the safety assessment of Iodopropynyl Butylcarbamate with the following conclusion: On the basis of the data presented in this report, the CIR Expert Panel concludes that Iodopropynyl Butylcarbamate is safe as a cosmetic ingredient at concentrations ≤ 0.1%. Iodopropynyl butylcarbamate should not be used in products intended to be aerosolized. The final report was published in 1998.

The lengthy discussion on which the Panel's conclusion is based occurred at the December 11-12, 1995 Panel meeting, during which the European Union's 0.1% concentration limit on iodopropynyl butylcarbamate in cosmetics was noted. Currently, the following 3 maximum authorized concentrations of this ingredient in cosmetics are in effect in the European Union, each of which is lower than the 0.1% limit previously determined: (1) rinse-off products (0.02%), (2) leave-on products (0.01%, except deodorants/antiperspirants), and (3) deodorants/antiperspirants (0.0075%). Furthermore, this ingredient is not to be used in oral hygiene and lip care products, and the following warning must be displayed on the label of rinse-off and leave-on cosmetic products that contain iodopropynyl butylcarbamate: Not to be used for children under 3 years of age. These restrictions deserve the Panel's consideration.

Included for your review is a copy of the Re-review document, the CIR report history, Literature search strategy, Ingredient Data profile, 2013 FDA VCRP data, Minutes from the December 11-12, 1995 (58th) and June 3-4, 1996 (59th) Panel meetings, a copy of the published final report, and use concentration data from the Council (data1 pdf file).

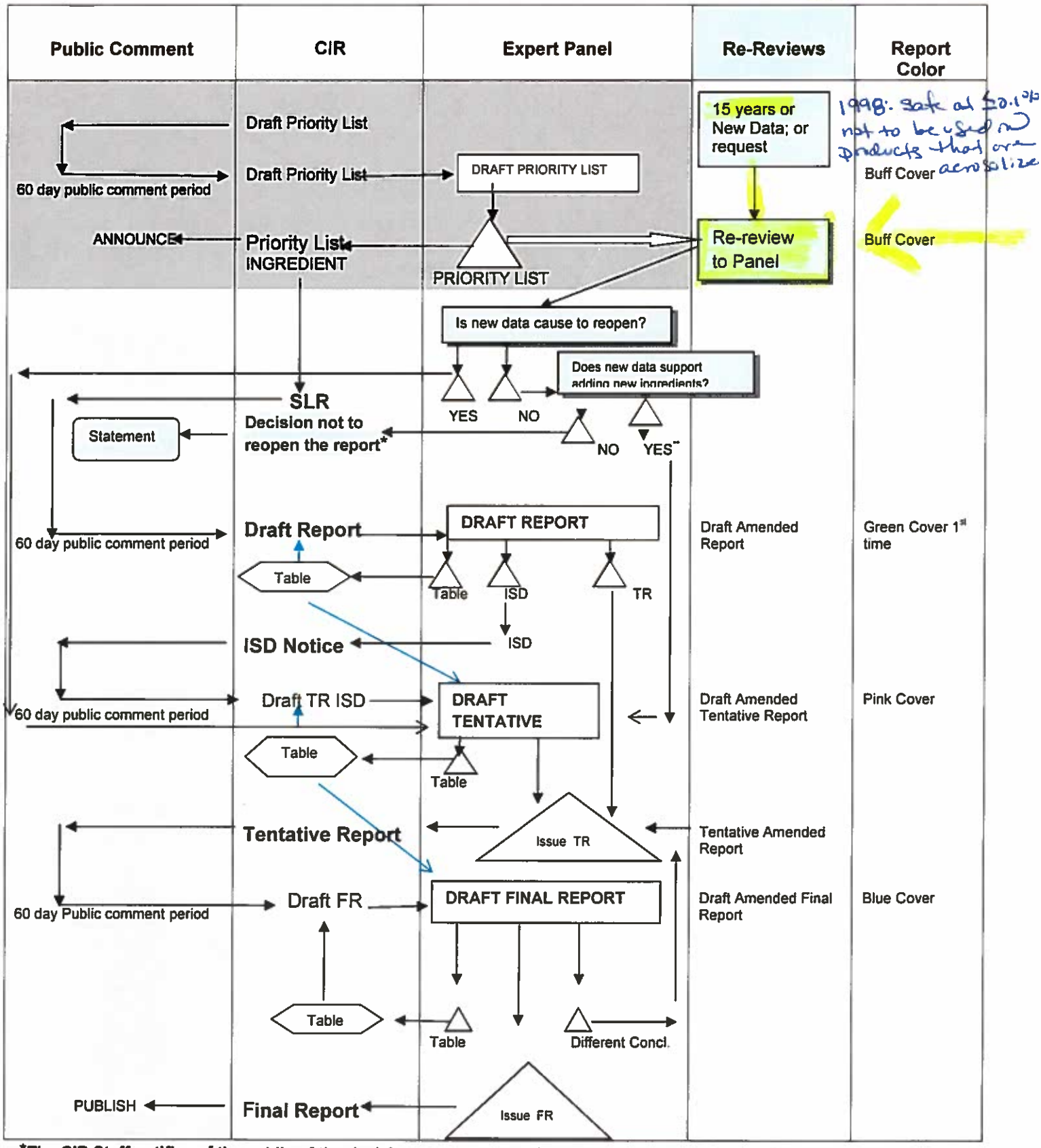
After reviewing the available data, the Panel needs to determine whether the final report on Iodopropynyl Butylcarbamate should be re-opened.

1101 17th Street, NW Suite 412, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

Iodopropynyl Butylcarbomate

SAFETY ASSESSMENT FLOW CHART

(Sept 2013)



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

CIR History of:

Iodopropynyl Butylcarbamate

At the June 3-4, 1996 Expert Panel meeting, the Panel issued a final report on the safety assessment of iodopropynyl butylcarbamate with the following conclusion: On the basis of the data presented in this report, the CIR Expert Panel concludes that iodopropynyl butylcarbamate is safe as a cosmetic ingredient at concentrations ≤ 0.1%. Iodopropynyl butylcarbamate should not be used in products intended to be aerosolized. The final report was published in 1998.

1st Re-review, Belsito and Marks Teams/Panel: September 9-10, 2013

December 11-12, 1995 (57th)CIR Expert Panel Meeting (Full Panel) – Day 2

Iodopropynyl Butylcarbamate

Dr. Belsito noted that his Team had concluded that Iodopropynyl Butylcarbamate is safe as used.

Dr. Schroeter indicated that his Team had restricted the final concentration of Iodopropynyl Butylcarbamate to 1%. This is based on human repeated insult patch test data. Furthermore, his Team determined that because of the danger of this compound (based on inhalation toxicity data) and the fact that it is used in an aerosolized product, that the report discussion should contain a caution statement.

Dr. Bailey said that most of the tests were conducted at concentrations much lower (0.125%) than the 1% limitation proposed by the Schroeter Team. He also noted that the EU has established a concentration limit of 0.1%, and that a limitation of 1% would be rather high.

Dr. Shank wanted to know the basis for the EU's concentration limit.

Dr. Bailey said that he did not know the basis for this limitation. However, he reiterated that most of the testing was done at a concentration of 0.125% in the data supplied.

Dr. Schroeter stated that the real risks with respect to safety are irritancy and sensitization and, with this in mind, 1% is an acceptable limitation.

Dr. McEwen said that he did not see a problem with establishing a concentration limit based on the available data or a conclusion of safe as used.

Dr. Belsito noted that comedogenicity had not been tested at concentrations greater than 1%. He said that a variety of data had been submitted, and that one does not know whether Iodopropynyl Butylcarbamate is toxic at concentrations greater than 1%, unless it is tested at these concentrations.

Dr. Belsito asked why the sensitization potential of Iodopropynyl Butylcarbamate is believed to be the only risk that this ingredient has.

Dr. Shank said that the other studies that were submitted give no indication that this ingredient poses a health hazard.

Dr. Belsito noted that comedogenicity was tested only at a concentration of 0.1%, and said that one does not know if Iodopropynyl Butylcarbamate is going to be comedogenic at a concentration of 1%. He also said that comedogenicity is a major issue for those using cosmetics.

Dr. McEwen said that the comedogenicity data involve concentrations that are above use levels.

Dr. Andersen noted that use concentrations of Iodopropynyl Butylcarbamate are considerably below 0.1%. In fact, most use concentrations are on the order of 0.01%.

Dr. Shank asked whether the use data are actual, because the Panel has received partial data on use concentrations.

Dr. Andersen said that the data represent approximately 40 formulations, and that the highest value was 0.0125%.

Dr. Shank asked if the Panel could rely on the concentration of use data as the actual use concentration range in industry today.

Dr. Andersen noted that the concentration of use data are 1995 data.

Dr. Shank recalled that these data were received from one company and wanted to know if Iodopropynyl Butylcarbamate is used by one company only.

Dr. McEwen said that the concentration of use data submitted are the only data in this area that CIR has, and that they were submitted in response to the Panel's request for data.

Dr. Shank confirmed with Dr. McEwen that these data don't necessarily represent the market.

Dr. Shank also noted that many studies on Iodopropynyl Butylcarbamate have been made available to the Panel, none of which suggests any problems. He said that the highest concentration (1%) that was tested well was tested in the human repeated insult patch test, and that the results were negative at this concentration.

Dr. Belsito said that any concentration limit should be established based on comedogenicity data. Therefore, the concentration limit should be set at 0.1%, the highest test concentration for comedogenicity. He mentioned that the argument relative to the toxicity of Iodopropynyl Butycarbamate was initiated because of a Hawaiian lawsuit over acneoform lesions of the back.

Dr. Shank reiterated that there is an excellent database on the toxicity of this ingredient, and that there are no data suggesting that Iodopropynyl Butylcarbamate is comedogenic.

Dr. Belsito said that the data do not suggest comedogenicity at concentrations up to 0.1%, the highest concentration that was tested.

Dr. Shank wanted to know why comedogenicity is a major concern.

Dr. Belsito said that comedogenicity is an issue that has been raised in association with Iodopropynyl Butylcarbamate, and that this is the weakest link with respect to setting a concentration limit. He noted that this ingredient is a halogenated compound, and that there are medical conditions that are known as iododerma and bromoderma.

Dr. McEwen suggested that the Panel consider setting a 0.1% concentration limit based on the comedogenicity data, and that any interested parties can respond to this limitation during the 90-day comment period to the Tentative Report.

The Panel voted in favor of issuing a Tentative Report with a conclusion indicating that Iodopropynyl Butylcarbamate is safe for use in cosmetics at concentrations of $\leq$ 0.1%.

Dr. Carlton abstained.

Dr. Schroeter said that a statement indicating that Iodopropynyl Butylcarbamate should not be used in aerosolized formulations should be included in the report discussion, in light of results in the acute inhalation toxicity studies.

Dr. Shank noted that his Team deleted one of the acute inhalation toxicity studies because of the number of animals used and the fact that the particle size was not included.

Dr. Schroeter noted that the case studies do not contribute to the safety assessment of Iodopropynyl Butylcarbamate and should be deleted from the report.

Dr. Andersen confirmed with Dr. Schroeter that the concern about aerosol use should be raised in the report discussion.

Referring to the carcinogenicity study included in the CIR report on Iodopropynyl Butylcarbamate, Dr. Slaga noted that a marked reduction in body weight was observed, and that the Schroeter Team had suggested that this be mentioned in the report discussion as follows: The two highest doses used in the carcinogenicity study suggest a toxic effect because there was a marked reduction in body weight.

Dr. Klaassen noted that the observation on weight loss is not important to the extent that this should be noted in the report discussion.

Dr. McEwen said that the marked reduction in body weight suggests that the MTD was exceeded.

On the subject of skin penetration, Dr. Schroeter said that the study using frozen cadaverous skin was less than adequate.

Dr. Jeffrey Yourick, with FDA, said that cadaverous skin probably gives a reasonable estimate of dermal absorption. He said that the use of cadaverous skin may be an important fact if the Panel considers the metabolism of Iodopropynyl Butylcarbamate to be important. In such a case, it would probably be essential to use viable skin.

Dr. Schroeter said that he was concerned about the use of viable skin because if Iodopropynyl Butylcarbamate were metabolized in any way, this might alter skin penetration.

Dr. Slaga said that, ideally, one would rather use live skin in any skin penetration study. He acknowledged that skin penetration studies involving frozen cadaverous skin have been done for years. Furthermore, if Iodopropynyl Butylcarbamate is going to be modified, there would be no indication of this when using cadaverous skin.

Dr. Belsito said that, in this situation, one is looking for absorption in an unmodified state. If the concern is modification in terms of carcinogenicity or end organ toxicity, such studies are available. He did not see the basis for rejecting the skin penetration data involving cadaverous skin (absorption, unmodified, through frozen cadaverous skin).

Dr. Schroeter said that he had not proposed deleting the *in vitro* skin penetration data. He reiterated that skin penetration studies on viable skin would have been preferable.

Dr. Bergfeld said that the fact that the Panel had a discussion on viable versus cadaverous skin should be noted in the meeting minutes. She also noted that the Panel had voted in favor of issuing a Tentative Report with the conclusion that Iodopropynyl Butylcarbamate is safe for use in cosmetics at concentrations of $\leq$ 0.1%. She said that the report discussion would be inclusive of today's Panel discussion plus a statement to the effect that Iodopropynyl Butylcarbamate should not be used in aerosolized products.

June 3-4, 1996 (59th)CIR Expert Panel Meeting (Full Panel) – Day 2

Iodopropynyl Butylcarbamate

Dr. Belsito noted that at the December 11-12, 1995 Panel meeting, the Panel voted in favor of issuing a Tentative Report with the following conclusion: On the basis of the data presented in this report, the CIR Expert Panel concludes that Iodopropynyl Butylcarbamate (IPBC) is safe as a cosmetic ingredient at concentrations of $\leq$ 0.1%. IPBC should not be used in products intended to be aerosolized.

Dr. Belsito also noted that information on methods of manufacture and a UV spectral analysis were received after the Tentative Report was announced, and that these data do not warrant substantively changing the Panel's conclusion.

The Expert Panel voted unanimously in favor of issuing a Final Report on Iodopropynyl Butylcarbamate with the conclusion stated above.

Iodopropynyl Butylcarbamate Check List for September, 2013. Analyst – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Iodopropynyl Butylcarbamate	X		X	X	X	X	X	X		X			X	X	X	X	X	X	X	X

Searches Performed: 6/27/2013
Search Updated: 7/26/2013
Database Searched: Scifinder

Search Terms (for years 1996-2013)

Iodopropynyl butylcarbamate
CAS No. 55406-53-6

Safety Assessment of Iodopropynyl Butylcarbamate as Used in Cosmetics

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INTRODUCTION

A Cosmetic Ingredient Review (CIR) Final Report with the following conclusion was published in 1998: On the basis of the data presented in this report, the CIR Expert Panel concludes that iodopropynyl butylcarbamate is safe as a cosmetic ingredient at concentrations ≤ 0.1%.[1] Iodopropynyl butylcarbamate should not be used in products intended to be aerosolized. The discussion from this final safety assessment is included at the end of this report. This re-review document contains the results of pertinent studies that became available after the final safety assessment was issued.

CHEMISTRY

Definition and Structure

Iodopropynyl butylcarbamate (CAS No. 55406-53-6) is the organic compound[2] that conforms to the structural formula in Figure 1. It is a solid with a melting point of 64.72 - 66.34 °C and a low vapor pressure of 0.000419 Pa.[3] The $\log K_{ow}$ of this chemical is 2.81, at 25 °C, and a water solubility of 223 mg/L is also reported.

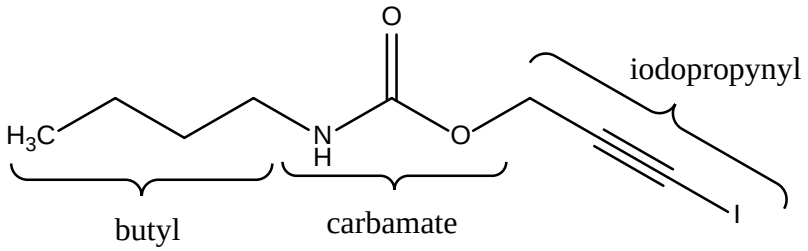

Figure 1. Iodopropynyl Butylcarbamate

Method of Production

The synthesis of iodopropynyl butylcarbamate can be achieved in two steps. 1.[4] The first of which is the reaction of phosgene with butylamine and propargyl alcohol. The product of this first step, propynyl butylcarbamate, is then iodinated with iodine monochloride.

USE

Cosmetic

Iodopropynyl butylcarbamate reportedly functions as a pesticide and preservative in cosmetic products.[2] According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2013, iodopropynyl butylcarbamate was being used in 942 cosmetic products.[5] These data are summarized in Table 1. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council (also included in Table 1) in 2013 indicate that iodopropynyl butylcarbamate was being used at concentrations up to 0.05% in cosmetic products.[6]

Cosmetic products containing iodopropynyl butylcarbamate may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

The following maximum authorized concentrations relating to the use of iodopropynyl butylcarbamate in cosmetic products marketed in the European Union are stated in the EEC Cosmetics Directive: (1) rinse-off products (0.02%), (2) leave-on products (0.01%, except deodorants/antiperspirants), and (3) deodorants/antiperspirants (0.0075%). Regarding

rinse-off products, iodopropynyl butylcarbamate is not to be used in mixtures for children under 3 years of age, except in bath products/shower gels and shampoo. Regarding leave-on products, iodopropynyl butylcarbamate is not to be used in body lotion and body cream, and is not to be used in mixtures for children under 3 years of age. Furthermore, iodopropynyl butylcarbamate is not to be used in oral hygiene and lip care products. The following warning must be displayed on the label of rinse-off and leave-on cosmetic products that contain iodopropynyl butylcarbamate: Not to be used for children under 3 years of age.[7]

Noncosmetic

Iodopropynyl butylcarbamate, as an antifungal preservative, has been approved by FDA for use as a component of adhesives that may be safely used as components of articles intended for use in packaging, transporting, or holding food.[8]

TOXICOLOGY

Repeated Dose Toxicity

Troysan polyphase p100 (98.7% pure iodopropynyl butylcarbamate) was evaluated in a repeated dose toxicity study involving groups of 10 New Zealand white rabbits (~ 4 months old; 5 males, 5 females per group).[3] Three groups received dietary concentrations of 500 ppm, 2,000 ppm, and 4,000 ppm, respectively, daily for 13 weeks. The control group was fed the same diet without the test substance. There were no treatment-related deaths in the study. Adverse effects were not observed in the 2 lower dose groups. In the 4,000 ppm group, the animals ate less and gained less weight during the early weeks of the study. Feeding with 4,000 ppm and 2,000 ppm resulted in the hepatic changes defined as slightly elevated GGT enzyme levels (at 4,000 ppm) and increased liver weights (at 2,000 ppm and 4,000 ppm, only in females). Microscopic changes in females in these 2 groups consisted of centrilobular hepatocellular enlargement (cell swelling) and brown pigment in the cytoplasm of hepatocytes, and sinusoidal macrophages. The no-observed-effect-level (NOEL) in this study was 500 ppm (~13 mg/kg/day).

Skin Sensitization

Iodopropynyl butylcarbamate, a biocide, was originally used for wood or paint preservation, but has been introduced as a preservative in cosmetics. The use of iodopropynyl butylcarbamate in cosmetic products has caused contact sensitization and allergic contact dermatitis. Although the risk of sensitization appears to be quite low, at concentrations up to 0.1% in cosmetic products, continued surveillance for iodopropynyl butylcarbamate allergy is necessary, as incidences of contact allergy may increase with increasing availability of iodopropynyl butylcarbamate-containing cosmetic products in the future.[9]

Iodopropynyl butylcarbamate (0.1%) in petrolatum) was tested on 4,883 consecutive patients for 18 months, between January of 1998 and June of 1999.[10] Regarding the MOAHLFA index (percentage of male, occupation, atopic dermatritis, hand dermatitis, leg dermatitis, face dermatitis, age > 40), the study comprised the following: 37% males, 17% with occupational dermatitis, 19% with atopic dermatitis, 31% with hand dermatitis, 10% with leg dermatitis, 17% with face dermatitis, and 61% were ≥ 40 years old. Patches were applied for 1 or 2 days, and reactions were scored according to both International Contact Dermatitis Research Group (ICDRG) and German Contact Dermatitis Research Group (DKG) recommendations, with obligatory readings at day 3 or day 4. At the day 3 reading, 0.3% were allergic to iodopropynyl butylcarbamate (14 + reactions; 2 ++ reactions). Doubtful or irritant reactions occurred twice as frequently. Patients patch tested for 24 h (n = 1814) reacted less frequently (0.1%) than the remaining patients patch tested for 48 h (0.5% of the patients). The reaction pattern was subsequently evaluated, after considering the possibility that a certain proportion of + reactions could have been false positives. More than 80% of the positive reactions displayed a crescendo or plateau time pattern. Eighteen of 43 doubtful reactions (?) appeared as late as day 3; these reactions could have been false negatives. The majority of doubtful reactions occurred earlier and had a decrescendo pattern, i.e., a typical irritant pattern. The authors concluded that the large proportion of doubtful (?) reactions may not only be due to the irritant potential of iodopropynyl butylcarbamate, but may also be due to test concentrations not being high enough to elicit an allergic reaction.

Patch test results were provided on metal workers who were suspected of having metalworking fluid (MWF) dermatitis.[11] In 2002 and 2003 combined, 16,848 patients were patch tested in various departments of dermatology comprising the Information Network of Departments of Dermatology (IVDK). Of these, 251 (1.5%) fulfilled the criteria of the study, and, thus, were included in the data analysis.Patch tests were performed and read, at least until day 3, according to both ICDRG and DKG guidelines. Patch test exposure time was 2 days in 208 patients (83%) and 1 day in 43 patients

(17%). Of the 251 metal workers, 206 were patch tested with the current MWF series, which included iodopropynyl butylcarbamate. Monoethanolamine ranked number 1 (11.6% positive reactions) among the current MWF allergens. Iodopropynyl butylcarbamate caused positive reactions in 0.5% of the patients.

To determine the concentration of iodopropynyl butylcarbamate that should be used in screening patch tests, an analysis was performed on data filed by 26 centers of dermatology (cooperating in the IVDK and the German Contact Dermatitis Research Group [DKG]) on patch tests performed with 1 or 2 concentrations of iodopropynyl butylcarbamate (0.1%, 0.2%, 0.3%, or 0.5%) in 8106 unselected patients.[12] Most centers used small Finn chambers on Scanpor, which remained in place for 1 or 2 days. The criteria used to determine the best test concentration of iodopropynyl butylcarbamate were: the reaction index, the positivity ratio, the rate of crescendo reactions, and the relationship between iodopropynyl butylcarbamate reactions and the MOAHLFA index irritant reactions to sodium lauryl sulfate (SLS), and allergic reactions to other contact allergens, including preservatives. Iodopropynyl butylcarbamate test concentrations of 0.1%, 0.2%, 0.3%, and 0.5% yielded 0.5%, 0.8%, 1.3%, and 1.7% positive reactions, respectively. However, this increase was accompanied by an even greater increase in doubtful and irritant reactions. Based on these figures and other criteria examined, it was suggested that the range of suitable test concentrations of iodopropynyl butylcarbamate should lie between 0.2% and 0.3%. A detailed analysis of MOAHLFA indices and of associations between reactions to iodopropynyl butylcarbamate and reactions to other allergens and to SLS showed that most of the positive reactions to 0.2% iodopropynyl butylcarbamate can be assumed to be allergic reactions. This analysis also showed that, with 0.2% iodopropynyl butylcarbamate, fewer false positive reactions can be expected when compared to 0.3% iodopropynyl butylcarbamate. The authors concluded that patch testing with 0.2% iodopropynyl butylcarbamate is suggested for patients with eczema, possibly related to preservatives.

The North American Contact Dermatitis Group (NACDG) tested iodopropynyl butylcarbamate (0.1% and/or 0.5% in petrolatum) between 1998 and 2008.[13] Patch tests were performed using Finn chambers on Scanpore tape. The patches remained in place for 48 h; reactions were scored initially at 48 h to 72 h, and, subsequently, between 72 h and 168 h after initial placement. Two patient groups of interest were defined, based on patch test reactions to iodopropynyl butylcarbamate, namely, weak (+) reactors and strong (++ or +++) reactors. Of the 25,321 patients tested, there were 226 (0.9%) weak reactors and 67 (0.3%) strong reactors. For iodopropynyl butylcarbamate-positive patients, the most frequent sites of dermatitis were scattered generalized distribution, hands, and arms. Most (> 50%) of the currently relevant reactions were to personal care products, and most reactions (> 90%) were not related to occupation. Only 4 of the strong reactors had definite clinical relevance, i.e., a positive use-test reaction or a positive patch-test reaction to a product containing iodopropynyl butylcarbamate. The frequency of positive reactions increased (0.25 vs. 1.5%) when the higher concentration (0.5%) of iodopropynyl butylcarbamate was used; however, most were weak reactions, of which some were likely irritant.

A study was performed to estimate the risk of sensitization to selected preservatives.[14] The occurrence of preservatives in 3541 leave-on products, based on the labeling of the ingredients, was documented. Frequency of sensitization to preservatives was analyzed on the basis of IVDK data for 2006-2009. As an estimate of sensitization risk, the sensitization exposure quotient (SEQ) was calculated as the quotient of the relative frequency of sensitization and the relative frequency of use. An SEQ of 3.4 was reported for iodopropynyl butylcarbamate. This SEQ may be compared with the value for phenoxyethanol (SEQ = 0.06, lowest SEQ reported in study) and the value for 2-bromo-2-nitropropane-1,3-diol (SEQ = 13, highest SEQ reported in study).

The thin-layer rapid user epicutaneous test (TRUE Test™) was investigated for its effectiveness in detecting allergic contact dermatitis.[15] This standard method for diagnosing allergic contact dermatitis in the United States consists of 3 panels containing 20 individual allergens and 8 allergen mixes. In this study, a retrospective analysis of 2088 patients who underwent patch testing between 1995 and 2010 was performed. Study groups were analyzed to determine whether positive reactions were to allergens and/or mixes present in the TRUE Test™ panels. All patients were tested using the Finn Chambers® technique. The patch panels were applied to the back, and reactions were scored on days 2 and 4 according to the NACDG scoring system. A score of 1, 2, or 3 was classified as positive. Iodopropynyl butylcarbamate was listed among the top 25 allergens and/or mixes, not contained in the TRUE Test™ series, that elicited positive reactions in the patient population. Of the 1091 patients patch-tested with iodopropynyl butylcarbamate, the percentage of patients with positive reactions was 2.2%. The percentage of positive patients whose reactions to iodopropynyl butylcarbamate were considered relevant was 75%.

The NACDG reported the results of patch tests performed from January 1, 2009 to December 31, 2010 at 12 centers in North America.[16] A total of 4,308 patients were tested. Patch tests were performed using Finn chambers on Scanpor tape. The patches remained in place for 48 h; reactions were scored initially at 48 h to 72 h, and, subsequently, between 72 h and 168 h after initial placement. The NACDG scoring system is defined in the preceding study. Of the 4,308 patients, 2,284 (46.3%) were diagnosed as having allergic contact dermatitis and 2,614 (60.7%) had at least 1 positive reaction. There were 6,855 positive reactions. When results were compared with the previous reporting period (2007-2008), a statistically

significant increase ($P < 0.05$) in the positive reaction rate was reported for the following 4 allergens: iodopropynyl butylcarbamate (tested at 0.5% in petrolatum), fragrance mix II (tested at 14% in petrolatum), propylene glycol (tested at 30% aqueous), and benzocaine (tested at 5% in petrolatum).

Case Reports

A 63-year-old male developed severe perianal and palmar contact dermatitis that was caused by sensitization to iodopropynyl butylcarbamate in moist sanitary wipes.[17]

A 58-year-old male worker in window-frame manufacturing company developed itch, scale, and fissuring of the hands over a 2-year period.[18] The wood (pine) used for window frame assembly had been treated with a preservative with the following composition: propiconazole (0.25%), tebuconazole (0.25%), and 3-iodo-2-propynyl butylcarbamate (0.2%) dissolved in white spirit. Patch testing with 0.1% 3-iodo-2-propynyl butylcarbamate yielded a ++ reaction on day 2.

A 20-year-old female presented with a 9-month history of recurrent, itchy facial dermatitis with associated periorbital swelling.[19] The patient had been using a cleansing wipe that contained iodopropynyl butylcarbamate and tea tree oil. The facial dermatitis resolved after use of the cosmetic cleansing wipe was discontinued. In patch tests, a Finn chamber® containing either ingredient was applied to the back using Scanpor® tape. A 3+ reaction to 0.1% iodopropynyl butylcarbamate was observed at days 2 and 4. A 2+ reaction to tea tree oil was also observed on days 2 and 4.

GENOTOXICITY

The genotoxicity of Troysan polyphase p100 (98.7% pure iodopropynyl butylcarbamate) was evaluated in the Ames test using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537, and TA1538. In the presence of metabolic activation, the test substance was evaluated at doses up to 1,000 µg/plate. Except for strain TA1535 (at doses up to 1,000 µg/plate), the test substance was evaluated at doses up to 333 µg/plate in the absence of metabolic activation. The negative control was dimethylsulfoxide (DMSO), and the following positive controls were used: 2-aminoanthracene, sodium azide, 9-aminoacridine, and 2-nitrofluorene. The test substance was not genotoxic with or without metabolic activation. Positive and negative control values were within normal ranges.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The developmental toxicity/teratogenicity of Troysan polyphase p100 (98.7% pure iodopropynyl butylcarbamate) was evaluated using groups of 20 female New Zealand White rabbits (weight range: 3 to 4 kg).[3] The 3 groups received oral doses (in corn oil; dose volume = 0.5 ml/kg) of 2, 20, and 50 mg/kg/day on gestation days 6 through 18. Twenty rats comprised the vehicle (corn oil) control group. Substantial toxicity was noted after dosing with 50 mg/kg/day; 2 females died and 1 (moribund) was killed between gestation days 21 and 23. Additional observations of maternal toxicity at the 50 mg/kg/day dose level included adverse clinical signs, body weight loss, and reduced food consumption. The clinical signs of toxicity at 50 mg/kg/day were: few feces, no feces, and soft stools. There were no adverse maternal effects in control or lower dose groups. One female in the 50 mg/kg/day dose group aborted on gestation day 24. There were no statistically significant differences in cesarean section parameters among the dose groups. However, at the 50 mg/kg/day dose level, there was a slight increase in mean post-implantation loss and a corresponding decrease in the mean number of viable fetuses. These differences occurred in the presence of substantial maternal toxicity. In all dose groups, there were no treatment-related fetal malformations or developmental variations during the study. The NOEL for maternal toxicity was determined to be 20/mg/kg/day, and the NOEL for teratogenicity was determined to be 50 mg/kg/day.

A teratological study on 3-iodo-2-propynyl butylcarbamate was performed.[20] Pregnant Wistar rats were treated orally with the test substance at doses of 0, 20, 60, or 180 mg/kg on days 7 to 17 of gestation. Cesarean sections were performed on day 20 of gestation. Transient swelling in the necks of pregnant rats was observed at doses of 60 and 180 mg/kg for 4 to 5 days after the first or second dose. Body weight gain, food intake, and adjusted body weight gain decreased, while increases in the maternal thyroid and stomach weights were observed at doses of 60 and 180 mg/kg. A decrease in the maternal thymus weight and an increase in maternal adrenal gland weight were observed at a dose of 180 mg/kg. The incidence of dead or resorbed fetuses and the sex ratio of living fetuses also increased at this dose level. There was no evidence of any treatment-related external, skeletal, or visceral abnormalities in fetuses. It was concluded that the no-observed effect levels for maternal and fetal toxicity were 20 mg/kg and 60 mg/kg, respectively.

DISCUSSION SECTION FROM CIR FINAL REPORT ON IODOPROPYNYL BUTYLCARBAMATE

The Cosmetic Ingredient Review (CIR) Expert Panel was concerned about the acute inhalation toxicity observed in animal studies with Iodopropynyl Butylcarbamate. The Panel thereby concluded that IPBC should not be included in cosmetic products meant to be aerosolized.

The Panel stated that skin penetration studies using viable skin are preferable to those using cadaver skin. Studies using cadaver skin measure penetration of unmodified compounds only, and do not provide information on the influence of other factors such as skin metabolism. Therefore, studies using viable skin are more useful in assessing the safety of cosmetic ingredients.

The Panel noted that dose-related reductions in body weight gain were observed in a long-term carcinogenicity study using Sprague-Dawley rats, although no evidence of carcinogenic potential was found. Although noting the low degree of sensitization observed in animal studies and in human repeated insult patch tests, the Panel acknowledged the mild dermal irritation potential of this ingredient. Because the highest concentration tested for comedogenicity was 0.1%, the Panel considered that concentration to be the highest for which the available data would support safety.

Table 1. Frequency and Concentration of Use According to Duration and Type of Exposure.[5,6]

	Iodopropynyl Butylcarbamate	
	# of Uses	Conc. (%)
Exposure Type		
Eye Area	45	0.009-0.023
Incidental Ingestion	NR	NR
Incidental Inhalation – Sprays	48	0.001-0.02
Incidental Inhalation - Powders	1	0.02
Dermal Contact	548	0.002-0.05
Deodorant (underarm)	NR	0.0075-0.02
Hair - Non-Coloring	374	0.00012-0.05
Hair-Coloring	14	0.0078-0.011
Nail	1	0.03
Mucous Membrane	102	0.015-0.05
Baby Products	14	NR
Duration of Use		
Leave-On	564	0.001-0.05
Rinse off	364	0.00012-0.05
Diluted for (bath) Use	14	0.015
Totals*/Conc. Range**	942	0.00012-0.05

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses
NOTE: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not be equal to sum total uses.

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2013 FDA VCRP Data

Iodopropynyl Butylcarbamate

01A - Baby Shampoos	1
01B - Baby Lotions, Oils, Powders, and Creams	1
01C - Other Baby Products	12
02B - Bubble Baths	14
03B - Eyeliner	10
03C - Eye Shadow	1
03D - Eye Lotion	14
03E - Eye Makeup Remover	8
03F - Mascara	5
03G - Other Eye Makeup Preparations	7
04A - Cologne and Toilet waters	8
04B - Perfumes	4
04E - Other Fragrance Preparation	8
05A - Hair Conditioner	87
05B - Hair Spray (aerosol fixatives)	5
05C - Hair Straighteners	2
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	80
05G - Tonics, Dressings, and Other Hair Grooming Aids	142
05H - Wave Sets	4
05I - Other Hair Preparations	52
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	12
06C - Hair Rinses (coloring)	1
06D - Hair Shampoos (coloring)	1
07C - Foundations	6
07F - Makeup Bases	1
08A - Basecoats and Undercoats	1
10A - Bath Soaps and Detergents	22
10E - Other Personal Cleanliness Products	66
11A - Aftershave Lotion	7
11D - Preshave Lotions (all types)	2
11E - Shaving Cream	3
11G - Other Shaving Preparation Products	2
12A - Cleansing	62
12C - Face and Neck (exc shave)	38
12D - Body and Hand (exc shave)	49
12F - Moisturizing	120
12G - Night	16
12H - Paste Masks (mud packs)	10
12I - Skin Fresheners	8
12J - Other Skin Care Preps	26
13A - Suntan Gels, Creams, and Liquids	3
13B - Indoor Tanning Preparations	20
Total	**942**

FINAL REPORT ON THE SAFETY ASSESSMENT OF IODOPROPYNYL BUTYLCARBAMATE (IPBC)[1]

Iodopropynyl Butylcarbamate (IPBC) functions as a preservative in a wide variety of cosmetic formulations. Although concentrations as high as 0.1% have been reported, most applications appear to require this preservative at less than 0.0125%. IPBC readily penetrates through the skin. The average acute oral LD_{50} in rats is 1.47 g/kg. Rats fed IPBC for 4 weeks had increased liver weights and decreased plasma cholinesterase activity, and rats fed IPBC for 13 weeks had transient behavior alteration, increased liver weights, hepatocyte enlargement, stomach lesions, and decreased weight gain. Rats administered IPBC as dusts and liquid aerosols had labored breathing—lung edema, emphysema, and reddened lungs were observed after exposure. Dermal irritation, but no evidence of skin sensitization, was seen in animal studies. At concentrations of 0.5%, IPBC caused iritis and conjunctival irritation in rabbit eyes, but exposure to concentrations up to 0.015% produced only slight conjunctival redness. IPBC was not genotoxic, with or without metabolic activation. No evidence of carcinogenic potential was found in a 104-week chronic oral toxicity study using rats. Reductions in weight gain were observed, along with inflammation of the nonglandular stomach and lesions in the submaxillary salivary gland. In reproductive and developmental toxicity studies using rats and mice, IPBC had no significant effect on fertility, reproductive performance, or on the incidence of fetal malformations. IPBC was found to be mildly irritating, but not sensitizing in clinical testing. At concentrations up to 0.1%, IPBC was not comedogenic in clinical tests. Given the acute inhalation toxicity observed in animals, the potential for mild irritation, and the absence of any data on comedogenicity at concentrations higher than 0.1% in clinical tests, the Expert Panel concluded that IPBC is safe as a cosmetic ingredient at concentrations $\leq$0.1%, but that it should not be used in products intended to be aerosolized.

Iodopropynyl Butylcarbamate (IPBC) functions as a preservative in cosmetic formulations. The following report reviews the published safety data available on IPBC.

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Rebecca S. Lanigan, former Scientific Analyst and Writer, prepared this report. Address correspondence to the Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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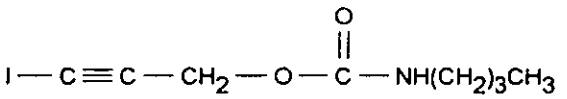

Figure 1. Chemical formula for Iodopropyl Butylcarbamate (IPBC).

CHEMISTRY

Definition and Structure

IPBC (CAS No. 55406-53-6) conforms to the formula shown in Figure 1 (Wenninger and McEwen 1993). Other technical names for IPBC include: Butyl-3-Iodo-2-Propynylcarbamate; Carbamic Acid, Butyl-3-Iodo-Propynyl Ester (Wenninger and McEwen 1993); 3-Iodo-2-Propynyl Butylcarbamate (Hansen 1984; Registry of Toxic Effects of Chemical Substances, 1995); Butyl-carbamic acid 3-Iodo-Prop-2-ynyl Ester (Scientific and Technical Information Network 1980a); 3-Iodo-2-Propynyl-*N*-Butyl-carbamate; and IPBC (Scientific and Technical Information Network 1980b). IPBC has several commercial names, including Glycacil (Wenninger and McEwen 1993) and Troysan Polyphase (Scientific and Technical Information Network 1980b).

Physical and Chemical Properties

IPBC is a white or slightly off-white crystalline powder of molecular weight 281, density 1.575 g/cm^3, and vapor pressure 2×10^{-6} mm Hg at 26°C. IPBC melts at 65–66°C (Hansen 1984; Henderson 1992) and decomposes at 100°C (Hansen 1984) to form carbon monoxide, carbon dioxide, nitrogen dioxide, dinitrogen oxide, and hydrogen iodide (Henderson 1992). At 54°C, the compound is stable (Henderson 1992). IPBC is only moderately soluble in water, but is highly soluble in acetone and benzyl alcohol, as well as other aromatic and polar solvents (Hansen 1984; Henderson 1992). The compound has low solubility in aliphatic solvents and hydrocarbon resins, and medium solubility in alkyd resins (Hansen 1984). IPBC (99.6% pure) in pH 5 buffered solution (at 25°C) is hydrolytically stable and does not degrade. At pH 7, the half-life of IPBC is 139 days, and the chemical is deiodinated to propargylbutylcarbamate, the only decomposition product detected (see Figure 2). IPBC at pH 9 has a half-life of less than one day (EPL Bio-Analytical Services,

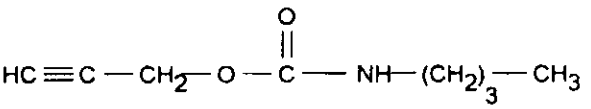

Figure 2. Propargyl butyl carbamate, the only decomposition product detected in the slow hydrolytic degradation of IPBC.

Table 1. Physical and chemical properties of Iodopropynyl Butylcarbamate

		Reference
Molecular formula	$C_8H_{12}INO_2$	Hansen 1984; Wenninger and McEwen 1993
Physical properties	White or off-white crystalline solid	Hansen 1984; Henderson 1992
Molecular weight	281	Hansen 1984
Melting point	65–66°C	Hansen 1984; Henderson 1992; Horn and Marutzky 1994
Boiling point	Decomposes at 100°C	Hansen 1984
Density	1.575 g/cm^3	Henderson 1992
Octanol/Water	646	Henderson 1992
Vapor pressure	2×10^{-6} mm Hg (26°C)	Hansen 1984; Henderson 1992
Solubility	Soluble in water; low solubility in aliphatic solvents and hydrocarbon resins; medium solubility in alkyd resins; high solubility in aromatic and polar solvents	Hansen 1984
	Water: 188 ppm at 25°C	Hansen 1984
	156 mg/L at 20–30°C	Henderson 1992
	0.016 g/100 g	G+G International Inc. 1995
	Mineral oil: 3.5 g/100g Isopropanol: 19.2 g/100g PEG monolaurate: 20.1 g/100g Dipropylene glycol: 20.5 g/100g Propylene glycol: 25.2 g/100g Ethanol: 34.5 g/100g Methanol: 65.5 g/100g	

Inc. 1990; Henderson 1992). The physical and chemical characteristics of IPBC are summarized in Table 1.

Photoreactivity

When exposed to ultraviolet (UV) light (290–400 nm) at room temperature and 65% relative humidity (intensity not given), ~25% of 400 ppm IPBC in ethanol (to give a 1% w/w concentration) decomposed, even after

400 hours of exposure. At 108 hours, the decomposition product peak appeared, and this product disappeared after 400 hours of irradiation. A secondary decomposition product became present at 270 hours (Lee, Tsunoda, and Takahashi 1991a). When irradiated, the carbon-iodine bond of IPBC is thought to be photolytically cleaved to release the iodine homolytically from the primary decomposition product and the iodine was then substituted for by hydrogen (Lee, Tsunoda, and Takahashi 1991b).

Method of Manufacture

IPBC is prepared by the iodination of terminal acetylenes (1-iodoalkynes). Commercially, IPBC is primarily manufactured using elemental iodine in a cold, aqueous hydroxide solution or by adding sodium hypochlorite to an alkali iodide solution. Refinements in the process give yields of 90–96% and make it possible to reach purities well above 98% (Rao and Periasamy 1995; G + G International, Inc. 1996).

Analytical Methods

IPBC can be determined by gas chromatography (GC) (Lee, Tsunoda, and Takahashi 1991a), GC/mass spectrometry (Lee, Tsunoda, and Takahashi 1991b; Horn and Marutzky 1994; G + G International, Inc. 1996), infrared spectrometry (G + G International, Inc. 1996), thin-layer chromatography (TLC), and electron capture GC (Gabriele and Iannucci 1984). IPBC in effluents and sediments can be extracted with methylene chloride, filtered, and dried. The residue is then dissolved in methanol and analyzed by high performance liquid chromatography (HPLC). HPLC has also been used to determine IPBC in water samples (Henderson 1992). IPBC in samples of wood preservative mixtures can be measured after combustion in a Parr oxygen bomb. An alkaline hydrazine solution converts any iodate present to iodide, the solution is titrated, and total iodine and chlorine can then be determined (Henderson 1992). Neutron activation analysis based on the specific radiations emitted by iodine atoms has been used to analyze wood samples for IPBC (Henderson 1992). IPBC has also been analyzed by an updated neutron activation and beta spectroscopy method using the I-128 isotope (Kennedy and Dai 1994; G + G International, Inc. 1996).

Ultraviolet Absorbance

The UV absorbance maximum of IPBC is below 350 nm (Gabriele and Iannucci 1984). The maximum absorbance for IPBC in 1 : 1 acetonitrile

and water solvent is 190 nm, with extinction coefficients of 6570 L/mol-cm (pH 5) and approximately 6000 L/mol-cm (pHs 7 and 9). A smaller peak occurs at 227 nm (500 L/mol-cm at pHs 5, 7, and 9). No other wavelength maxima were observed between 190 and 800 nm (Ricerca, Inc. 1994). UV spectroanalysis of IPBC in methanol had two peaks: one smaller peak was located at 230.5 nm and a larger shoulder at 200 nm with a valley at 218.5 nm. A peak at approximately 195 nm was identified as being solvent related (G + G International, Inc. 1996).

Impurities

Technical grade IPBC is 97–99% pure (Henderson 1992; G + G International 1995). Primary impurities are sodium chloride (0.9% maximum) and triiodoallylbutylcarbamate (<0.1%) (Henderson 1992).

USE

Cosmetic

IPBC is used as a preservative in cosmetic formulations (Wenninger and McEwen 1992). It was reported to be used in 122 formulations as of January 1996 [Food and Drug Administration (FDA) 1996] in a wide range of products, as detailed in Table 2. Concentrations of use are no longer reported to the FDA by the cosmetic industry (FDA 1992) and no concentration data were available for IPBC prior to 1984.

Data submitted by G + G International, Inc. (1995) stated that 0.025–0.1% IPBC is typically used in cosmetic formulations. Product use data were submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in 1995. IPBC was used at 0.005–0.0125% (w/v) in facial moisturizers, 0.01–0.0125% in sunscreen and sunless tanning formulations, 0.0125% in facial cleansers, and 0.005–0.01% in after shave formulations.

International

Use of IPBC as a preservative in cosmetics within the European Communities was provisionally approved for use until June 30, 1996, at concentrations no higher than 0.1% (Dupuis 1994); the ingredient has since been approved and given the EU/COLIPA chemical code number P 91 (G + G International, Inc. 1995). IPBC is also on the German official "Blue List" (code P 245) as being approved for use in cosmetics (Ippen 1993). IPBC is not listed in the *CTFA List of Japanese Ingredients* (Rempe and Santucci 1992).

Table 2. Cosmetic formulation data on Iodopropynyl Butylcarbamate (FDA 1996)

Product category	Total no. formulations in category	Total no. of formulations containing ingredient
Other fragrance preparations	195	2
Hair conditioners (noncoloring)	715	14
Shampoos (noncoloring)	972	47
Tonics, dressings, and other hair grooming aids	604	8
Other hair preparations (noncoloring)	395	4
Hair dyes and colors	1612	8
Hair shampoos (coloring)	29	2
Other manicuring preparations	83	1
Aftershave lotion	268	8
Other shaving preparation products	63	4
Cleansing preparations	820	2
Face and neck preparations (excluding shaving preparations)	300	2
Body and hand preparations (excluding shaving preparations)	1012	2
Moisturizing preparations	942	5
Night preparations	226	2
Paste masks (mud packs)	300	1
Other skin care preparations	810	3
Suntan gels, creams, and liquids	196	1
Indoor tanning preparations	67	5
Other suntan preparations	68	1
1996 total		**122**

Noncosmetic

The main noncosmetic uses of IPBC rely upon its antifungal activity. In October 1988, IPBC was petitioned for use as an antifungal preservative in foods (FDA 1988; Rothschild 1990). IPBC is registered as an antimicrobial with the U.S. Environmental Protection Agency and the Canadian Environmental Protection Division, which set an Acceptable Daily Intake by humans of 2.80 mg/day for a 70-kg person based on intake by rats (Henderson 1992). IPBC has been used as a consumer and industrial fungicide in the production of paints (Machemer 1979; Hansen 1984; Henderson 1992), vinyl wallpapers, wallpaper adhesives

(Machemer 1979; Henderson 1992), metalworking fluids, canvas, and cordage (Henderson 1992). IPBC applied to wood or timber with brush treatment at 0.75% (w/w) or by vacuum/soak impregnation protects against the fungi *Coriolus versicolor*, *Tyromyces palustris*, and *Serpula lacrymans* (Lee, Tsunoda, and Takahashi 1990a, 1992). IPBC had a synergistic effect when a surface-active agent was also applied to the wood, and protected against every wood-decaying fungus tested (Hansen 1984; Lee, Tsunoda, and Takahashi 1990b). Approximately 50 ppm (0.005%) IPBC controlled fungal growth and 250–1000 ppm provided bactericidal protection (G+G International, Inc. 1995). Bacteria controlled by IPBC included *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeroginosa*. The minimum inhibitory concentrations (MIC) of IPBC (agar inhibition tests) for a variety of microorganisms were submitted by industry. The MICs of IPBC for common molds, mildews, yeasts, and fungi ranged from 0.6 ppm (*Aspergillus niger*) to 10 ppm (*Trichoderma viride*). For algae, the MICs were below 50 ppm (G+G International, Inc. 1996).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

In rats, ^{14}C-IPBC was quickly absorbed from the intestinal tract to the bloodstream when administered orally as a suspension in 0.5% carboxymethylcellulose. The compound was then rapidly eliminated. Peak plasma concentrations occurred at 2 hours postdose, and 23–36% of the parent dose was bound to plasma proteins. Radioactivity in the liver and kidney decreased steadily up to 240 hours postdose, but in skeletal muscle, lungs, and heart, the decrease was slower. From 12 to 240 hours after administration, radioactivity in fat tissue and skin remained relatively constant. At 1 hour after intravenous administration (dissolved in 1 : 1 ethanol : water), very little IPBC was detected in the plasma (Henderson 1992).

In TLC analysis of plasma and urine, 3-4 and 4-5 metabolic peaks were found, respectively. The urine profile also included 2-3, so-called "plasma-type" metabolites, but none of the metabolic products were identified (Henderson 1992).

Plasma radioactivity, excretion, retention, and protein-binding studies were performed on 150 to 250-g Sprague-Dawley CD rats. ^{14}C-IPBC was administered either orally (20 and 125 mg/kg) or intravenously (0.5 mg/kg). Radioactivity was quickly eliminated from plasma, and IPBC was possibly absorbed in the gastrointestinal tract. ^{14}C in the body decreased in most tissues after dosing, but a significant amount of radioactivity was retained by fat tissue and a smaller amount by skin and skeletal muscle. IPBC was metabolized to $^{14}CO_2$ rapidly, as well as

other unidentified polar compounds; 32.3–50.9% of the parent dose of IPBC was excreted in urine and 38.2–56.7% in the exhaled air. Small amounts were also eliminated in the feces and/or retained in the body (Hazleton Laboratories, Deutschland 1987; Henderson 1992).

3-Iodo-2-[^{14}C]-propynyl-*N*-[1-^{14}C]-butylcarbamate-treated human skin samples (400–800 μm diameter, epidermis and papillary dermis) were evaluated to determine the potential for systemic exposure from IPBC. A dose of 5 μl of 0.1% radioactive IPBC in acetone was applied to six previously frozen skin samples (epidermis and papillary dermis), 400–800 μm thick, from each of four cadavers. Each skin sample was exposed to a dose of 6 μg/cm^2 so that approximately 0.5 μCi was applied to each. The contact area size was 0.8 cm^2. At 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours after treatment, the amount of radioactivity in the receptor fluid was measured. At the time of the last measurement (24 hours), excess radioactivity on the epidermal skin surface was removed and the amount remaining in the epidermis and dermis measured. Also, the evaporating radioactivity was trapped as it escaped the epidermal surface, and was quantitated. Skin penetration, a sum of the total radioactivity in the receptor fluid and dermis, was recorded as a percent of the applied dose. In this study, $53 \pm 14\%$ of the applied radioactivity penetrated the skin within 24 hours, and the peak penetration occurred within 8 hours of the application of IPBC. About $14 \pm 5\%$ evaporated from the skin surface during the course of the study. Approximately $87 \pm 10\%$ of the applied radioactivity was recovered during the test (Reifenrath Consulting and Research 1995).

Pharmacologic Effects

Carbamate compounds other than IPBC have been implicated in the inhibition of blood acetylcholinesterase activities. This inhibition results in the accumulation of the neurotransmitter acetylcholine, so that the nerves are overstimulated. Adverse effects can then occur in the central and autonomic nervous systems and at neuromuscular junctions (Henderson 1992).

In order to determine the potential effects of IPBC on the blood plasma enzyme, a cholinesterase inhibition study was performed using Sprague-Dawley rats. Ten rats per sex per dose made up each group in the study. Male (176–190 g) and female (163–196 g) rats received 0, 2, 4, 10, or 16 mg/kg IPBC in polyethylene glycol in water via the lateral tail vein. Blood samples were drawn at 15 and 30 minutes, 1, 2, and 5 hours post-dose and analyzed for erythrocyte cholinesterase. A variation in erythrocyte activity was detected between individual rats, but no changes in cholinesterase activity occurred as a result of treatment with up to 16 mg/kg IPBC (Inveresk Research International, Ltd. 1988a).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Technical grade (in this case, 97% pure) IPBC has an average acute oral LD_{50} of 1470 mg/kg in rats (Hazleton Laboratories America, Inc. 1984; Henderson 1992). The LD_{50} after a 14-day observation period was 1056 mg/kg and 1795 mg/kg in female and male rats, respectively (Hazleton Laboratories America, Inc. 1984; Henderson 1992), to give a toxicity rating of 3 (moderately toxic) to the compound. Another source reported that technical grade IPBC has an acute oral LD_{50} of 1580 mg/kg in rats, but no experimental details were given (Hansen 1984).

Adult albino Sprague-Dawley rats weighing 200–250 g each were allotted into groups of five males and five females per sex, per dose. Each rat received a 10 ml/kg suspension of IPBC in Duke's pure corn oil by gavage. Doses were 250, 500, 1000, 1500, or 2000 mg/kg. Rats in all groups had rough coats. All groups except for the 1000 mg/kg dose group were observed to have soft feces and urine stains, as well as slight depression. The rats that were administered 1500 mg/kg had red stains on the nose and/or eyes (Hazleton Laboratories America, Inc. 1984).

Male and female Sprague-Dawley rats received by gavage single doses of undiluted cosmetic formulations containing various concentrations of IPBC from 0.0100–0.0150% w/v and were killed for necropsy on day 7 or 8 of the studies, summarized below.

Moisturizing gel, sunscreen lotion, moisturizing cream, and moisturizing gel containing 0.01% IPBC each caused no unscheduled mortality or changes in body weight in 10 rats tested per preparation. The acute oral LD_{50} of each formulation was >10,000 mg/kg with 95% confidence (Springborn Laboratories, Inc. 1992a, 1993a, 1993b). Administration of the moisturizing gel resulted in dark material around the facial area in 2/10 rats, ocular discharge in 1/10 rats, and enlarged cervical lymph nodes in 3/10 dosed rats (Springborn Laboratories, Inc. 1993a). Dosing with sunscreen lotion resulted in dark material around the nose (2/10) and fecal stains (1/10) (Springborn Laboratories, Inc. 1993b). No clinical abnormalities were observed when the other formulations were administered (Springborn Laboratories, Inc. 1992a).

Sunscreen lotion and cream each containing 0.0125% IPBC had an acute oral LD_{50} >10,000 mg/kg, with no mortality or changes in body weight gain when a 10 g/kg dose of each formulation was administered to three rats per sex (Springborn Laboratories, Inc. 1991a, 1991b). Sunscreen lotion and cream (0.0150% IPBC), administered as 2 g/kg doses to three rats per sex, each had an LD_{50} >2 g/kg. One male that received sunscreen lotion had soft stool from $2\frac{1}{2}$ to 4 hours postdosing, but no

other clinical signs were reported (International Research and Development Corp. 1990a).

Dermal

Adult male New Zealand white rabbits, each weighing 2.3–3.0 kg, were divided into two groups of five rabbits each. The first group had abraded skin, and the second nonabraded skin. IPBC at 2 g/kg was moistened with physiologic saline prior to dermal application. All rabbits were observed for 14 days after the 24-hour exposure period. No deaths were reported in either group during the study. Erythema and edema were observed at the treatment sites in all rabbits during the 24-hour exposure period (Bioassay Systems Corp. 1984a). The LD_{50} was greater than 2000 mg/kg in male rabbits (Hansen 1984; Bioassay Systems Corp. 1984a; Henderson 1992) to give a corresponding toxicity rating of 3 (Henderson 1992).

Inhalation

Various concentrations of IPBC were administered as dusts and liquid aerosols to seven groups of five Sprague-Dawley rats per sex per group, each rat weighing 199–322 g. The first four groups inhaled IPBC as a dust (average mass median aerodynamic diameter of 4.3 μm; average geometric standard deviation of 2.9; average of 82% of particles $\leq$10 μm), receiving gravimetric concentrations of 1.7, 0.38, or 0.72 mg/L, respectively. The remaining four groups received 3.4, 1.8, 0.45, or 0.75 mg/L, respectively, as a liquid aerosol (average mass median aerodynamic diameter of 2.4 μm; average geometric standard deviation of 2.7; average of 94% of particles $\leq$10 μm). All groups that inhaled IPBC had decreased activity, eye closure, and excessive lacrimation. When removed from the test chamber, signs in the survivors (number not given) included labored breathing, gasping, and secretory discharges during the first week after exposure. These signs of toxicity generally diminished in the survivors after that time. Edema, emphysema, and reddened lungs were observed during post mortem examinations. The LC_{50} for IPBC as a dust was 670 mg/m^3 for both male and female rats (680 mg/m^3 average). As a liquid aerosol, the LC_{50} was 630 mg/m^3 for male and 990 mg/m^3 for fem-ale rats (780 mg/m^3 average) (Biodynamics, Inc. 1990).

Short-Term Toxicity

Rats were fed 60, 125, or 250 mg/kg/day IPBC for 4 weeks (method and other details were not specified). Rats in the high-dose group had decreased weight gain and feed intake, and the females had decreased plasma cholinesterase activity and increased liver weights. Similar

effects occurred in rats fed 125 mg/kg/day. In the low dose group, only a slight increase in relative liver weight was observed (Henderson 1992).

In a range-finding reproduction study, mated female rats that received 80 mg/kg/day IPBC by gavage for 20 days of gestation had no lesion at necropsy. In a related study, males fed 700 ppm IPBC for 28 days had no signs of toxicity (Henderson 1992).

Subchronic Toxicity

Sprague-Dawley rats (number not given) received 20, 50, or 125 mg/kg IPBC in corn oil five times per week as part of a 13-week feeding study. Rats administered 125 mg/kg had transient behavior alteration, increased liver weights, and hepatocyte enlargement. Males of this dose group had decreased weight gain and gastric lesions. Transient behavioral alterations and increased relative and absolute liver weights also were recorded in both sexes at 50 mg/kg. The no-observed-adverse-effect level (NOAEL) was 20 mg/kg. After a 4-week recovery period, no treatment-related pathologic changes were observed, indicating that the lesions were reversible. IPBC and/or the test vehicle were only slightly irritating to the rat when administered orally (Henderson 1992).

Groups of 28-day-old Sprague-Dawley rats were administered IPBC in corn oil by gavage for 13 weeks in a 90-day subchronic oral toxicity test. Ten males and 10 females, weighing 217–280 g and 140–191 g at initiation, respectively, made up each of five groups. IPBC (0, 4, 10, or 25 mg/ml) in corn oil, with a dose volume of 5 ml/kg, were tested. Doses of 20, 50, and 125 mg/kg were administered five times per week for 13 weeks. No deaths were reported during the study. No toxic effects were seen in females administered 125 mg/kg or males given 50 mg/kg. No changes in either hematology or clinical chemistry parameters (biochemistry and urinalysis) or gross lesions were observed. Male rats given 125 mg/kg had depressed body weight gain, hepatocyte enlargement, and increased liver weights (Bioassay Systems Corp. 1984b).

Undiluted sunscreen lotion containing 0.0125% IPBC was applied dermally to the shaved backs of New Zealand white rabbits. A dose of 2 ml/kg/day applied 5 days per week for 13 weeks caused no signs of systemic toxicity, but did induce slight dermal irritation. Control rabbits had distilled water applied to the test sites. At the start of the study, all rabbits were 3–4 months of age and each group contained five males and five females. Detailed observations were made once daily, whereas clinical condition (mortality, moribundity, and overt toxicity) and dermal irritation were scored twice daily. Body weights were determined prior to the first treatment, and then once a week for the duration of the study. At the end of week 13, the rabbits were killed for necropsy. No

unscheduled deaths occurred, and no differences in mean body weight and body weight gain were found between test and control groups. Rabbits (5/10) had slight to moderate erythema that appeared initially at day 6 and cleared by day 48. One rabbit had sporadic erythema throughout the study. Rabbits (2/10) had slight to moderate edema that cleared by day 52. In a few rabbits, desquamation, fissuring, and red raised areas were occasionally observed. No differences in hematologic values were present. At necropsy, 2/10 rabbits had mild erythema or red discoloration of the application site. Neither gross lesions nor organ weight differences were noted. Microscopic changes that were attributable to the application of the test material were acanthosis and hyperkeratosis of the epidermis and chronic inflammation of the dermis (International Research and Development Corp. 1994a).

In a similar study, moisturizer containing either 0.0125% or 0.6250% IPBC in an oil/water emulsion caused no signs of systemic toxicity when applied to 10 New Zealand white rabbits (International Research and Development Corp. 1994b).

Chronic Toxicity

Male and female 4-week-old Sprague-Dawley rats, 200 of each, were used in a 104-week chronic oral toxicity study. Fifty rats of each sex were in each group, including the control. At study initiation, males weighed approximately 85 ± 5 g and females 60 ± 5 g. IPBC was administered in the diet, which was offered ad libitum, at 20, 40, or 80 mg/kg/day. IPBC concentration was adjusted weekly for the first 13 weeks of the study, then once every 4 weeks to ensure that the dose was constant for the duration of the experiment. All rats were necropsied at the end of the study. Deaths included 22 males and 17 females in the untreated group; 20 males and 21 females of Group 2 (20 mg/kg); 24 males and 10 females of Group 3 (40 mg/kg); and 14 rats of each sex of Group 4 (80 mg/kg). No evidence of carcinogenic potential was found, and the NOAEL was 20 mg/kg/day for both sexes. No significant differences occurred between groups, and no clinical signs were observed due to the dietary addition of IPBC. Body weight gain decreased in the dosed males, from a slight reduction in the 20 mg/kg dose group, to a marked reduction in the 80 mg/kg group. Females administered 40 mg/kg and 80 mg/kg had moderate and marked reductions in body weight gain respectively. The 80 mg/kg-dosed males had slightly lower feed consumption, but no differences were observed in water consumption between groups. Differential blood counts and organ weights did not differ between the control and dose groups. The 40 mg/kg males and 80 mg/kg males and females had increased incidences of gastric lesions. Rats of both sexes given 40 and 80 mg/kg/day also had lobular degeneration of the submaxillary

salivary gland, submucosal edema, and inflammation (in the nonglandular portion) of the stomach. Acanthosis, hyperkeratosis, ulceration, basal cell proliferation, and lesions associated with ulcers were also observed in the nonglandular stomach in those two groups (Inveresk Research International 1989a).

Dermal Irritation

Primary skin irritation and corrosion tests were performed on six male New Zealand white rabbits weighing between 2.0 and 3.5 kg. A dose of 0.5 ml IPBC was applied to two 1″ × 1″ sites, one abraded and one unabraded for a 4-hour exposure time. Skin sites (under occlusive patches) were observed and rated at 4, 24, 48, and 72 hours after administration. At the end of the 4-hour period, slight erythema and severe edema were observed, but recovery was complete by 48 hours. The primary irritation index was 0.50 and IPBC was noncorrosive (Bioassay Systems Corp. 1981a).

In a similar study, slight to moderate erythema and slight edema were noted in two rabbits (total number not given) that had been exposed to IPBC (concentration not given) under a semiocclusive patch for 4 hours. The reactions occurred at 24 hours after patch removal. Slight erythema persisted until the 72-hour assessment in one of the affected rabbits. Investigators concluded that IPBC is slightly irritating to rabbit skin (Inveresk Research International, Ltd. 1989b).

Dermal Sensitization

Henderson (1992) reported that IPBC (concentration not given) produced slight irritation when applied to the skin of rabbits and that the compound was not a dermal sensitizer in guinea pigs. Hansen (1984) stated that a 40% solution of IPBC was not a skin sensitizer. No other details were given.

Female albino Dunkin-Hartley guinea pigs were used in a Magnusson-Kligman Maximization Test to determine the potential for development of contact hypersensitivity following intradermal and topical (occlusive patch) application of IPBC. Twenty guinea pigs served as controls. The test group of 40 guinea pigs received three pairs of intradermal injection: the first was Freund's complete adjuvant diluted 1 : 1 with water; the second was 10% (w/w) IPBC in propylene glycol, and the third was 20% IPBC in Freund's complete adjuvant (1 : 1). Seven days after administration of the injections, 0.45 ml of 50% (w/w) IPBC in petrolatum was applied topically for 48 hours. Three weeks after induction, a topical challenge of 0.1 g of 0.01% (w/w) IPBC in petrolatum was administered to the guinea pigs. No evidence of delayed contact hypersensitivity was observed (Scantox Biological Laboratory, Inc. 1989).

Ocular Irritation

The potential for IPBC to produce ocular irritation in young adult New Zealand white rabbits was determined by testing 0.5% IPBC in corn oil and 0.5% in a typical baby shampoo formulation. Twelve rabbits were divided into two groups of three males and three females each. Group 1 received 0.1 ml IPBC in corn oil (right eye) and corn oil (left eye). The second group was administered IPBC in baby shampoo (right) and baby shampoo alone (left). The eyes of all rabbits were rinsed 24 hours after application and were evaluated at 1, 24, 48, and 72 hours, 4 and 7 days. IPBC in corn oil and corn oil alone produced no eye irritation. Iritis and conjunctival irritation were produced in rabbits administered IPBC in baby shampoo and baby shampoo alone. This irritation cleared within 7 days after exposure. No apparent differences between responses were observed in Group 2 rabbits for shampoo plus 0.5% IPBC and shampoo alone (Hill Top Biolabs 1991).

In another study, nine male New Zealand white rabbits weighing 2.0–3.5 kg were treated with 0.1 g IPBC, six rabbits without irrigation, and three with irrigation. The test substance was applied to one eye of each rabbit, and the other eye served as control. Severe hyperemia, chemosis, discharge, and corneal opacity were observed in unrinsed eyes. In five of six rabbits, the iris appeared congested and unreactive to light. In rinsed eyes, discharge was slight in two of three rabbits. Except for one rabbit, which still had corneal opacity, effects subsided by day 21 after exposure in rabbits with unrinsed eyes. In the other group, the effects were no longer observed after 2 days (Bioassay Systems Corp. 1981b).

A dose of 0.055 g (0.1 ml) IPBC was instilled into the conjunctival sac of each of nine New Zealand white rabbits. The contralateral eye served as the untreated control. At 30 seconds postinstillation, the eyes of three rabbits were rinsed with 50 ml of physiologic saline. All eyes were examined for up to 21 days after dosing. Substantial injury occurred in the unrinsed group; 6/6 eyes had corneal opacity by the 24-hour scoring interval. The corneal injury was associated with corneal epithelial sloughing, and was confirmed by positive fluorescein dye retention. Normal background retention (stippling) was observed in 3/6 test eyes, but was not considered significant. Opacity persisted until the last test day, and was accompanied by corneal vascularization. Iritis was observed in 6/6 of the test eyes at 1 hour postdose and resolved by day 21. Conjunctivitis (6/6) was observed at 1 hour as well, diminished throughout the test period, and persisted until day 21. Two-thirds of the rinsed eyes at 1 hour had iritis that resolved by 48 hours. Conjunctival irritation (2/3) occurred at the same time and resolved by day 7. In the remaining rabbit's rinsed eye, responses resembled those of the rabbits with unrinsed

eyes, but all reactions had resolved by day 21. As a result of this study, investigators reported that IPBC was a severe irritant to the eyes of rabbits (Springborn Laboratories, Inc. 1990).

Undiluted sunscreen lotion, moisturizing cream, and moisturizing lotion were each instilled directly onto the cornea of the right eyes of three New Zealand white rabbits. A 10 μl dose of each formulation did not produce corneal opacity, iritis, or conjunctivitis as evaluated at 24 hours after dosing (Springborn Laboratories, Inc. 1992b, 1993c).

In similar studies, 10-μl doses of undiluted facial cleaner, sunscreen lotion, and sunscreen cream, each containing 0.0125% IPBC, were instilled into conjunctival sacs of New Zealand white rabbits (Springborn Laboratories, Inc. 1991c, 1991d, 1991e, 1993d, 1994a). In one study, the facial cleaner did not cause ocular irritation (Springborn Laboratories, Inc. 1993d), but in another, 2/3 tested eyes had conjunctivitis at 24 hours after dosing, which cleared at 72 hours (Springborn Laboratories, Inc. 1994b). Sunscreen lotion produced conjunctival redness in 3/3 test eyes, which resolved by 48 hours (Springborn Laboratories, Inc. 1994a), but in an earlier study it did not result in ocular irritation (Springborn Laboratories, Inc. 1991c). In a third study, 1/3 eyes had conjunctival redness (Springborn Laboratories, Inc. 1991d). Sunscreen cream did not produce ocular irritation (Springborn Laboratories, Inc. 1991d, 1991e).

Instillation of 10-μl doses of sunscreen lotion and cream (0.0150% IPBC) resulted in slight conjunctival redness in 1/3–2/3 eyes (International Research and Development Corp. 1990b). No ocular irritation was observed in a similar study (International Research and Development Corp. 1990c).

Photosensitization

Male and female 300–500 g Hartley guinea pigs (37 of each) were challenged with 5% IPBC to determine delayed contact hypersensitivity and/or photosensitization potential. Test groups were 22 males and 22 females, and 30 guinea pigs served as controls, with 3,3,4,5-tetrachlorosalicylanide as the positive control material. In the test group, seven guinea pigs per sex were tested for primary irritation, five per sex for induction, primary challenge, and rechallenge; five untreated guinea pigs per sex for primary challenge, and five untreated per sex for rechallenge. For induction, a site adjacent to the one used for primary challenge and rechallenge was used. The period between primary challenge and rechallenge was seven days. In an adaptation of the Buehler method, 5% IPBC in polyethylene glycol 400 (0.3 ml per 25 mm application site) was applied topically to the dorsal surface of the guinea pigs and the sites covered with occlusive patches for 4 hours after administration of the test chemical. IPBC was reapplied three times per

week (Monday, Wednesday, and Friday) for three consecutive weeks. At 30 minutes after removal of the occlusive dressing, 20-watt black light bulbs were used to irradiate the guinea pigs with UVA and UVB light for 2 hours each time. Exposure intensity peaked at 365 nm for UVB and 310 nm for UVA. Application sites were observed and evaluated at 24 and 48 hours after the removal of the occlusive dressings for signs of irritation. Photosensitization was not produced by 5% IPBC. Three guinea pigs in the induced group had grade 1 (slight) irritation, whereas guinea pigs in the untreated group had grades of ± after primary challenge. Due to these questionable findings, a rechallenge was performed. Maximum skin reaction grades of ± were observed in both induced and noninduced primary challenge groups, establishing that photosensitization did not occur (Hill Top Biolabs 1994).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

IPBC was administered to Sprague-Dawley rats by diet to determine its effects on the P and F_1 generations, as well as their offspring, F_{1a} and F_{1b}. Each of four groups included 50 rats, 25 male and 25 female. P males and females weighed 175–235 g and 140–85 g, respectively. Rats were fed diet containing 120, 300, or 750 ppm IPBC for 293 days. Test and control diets were available to the rats ad libitum. At the conclusion of the dosing period, the rats were killed for necropsy. No treatment-related effects were observed in clinical condition, necropsy findings, fertility, mating performance, postnatal viability, or postnatal growth. Physical and functional development were similar to controls. The mean feed consumption of 750 ppm-dosed P and F_1 males decreased slightly during the rats' premating period. During the same period, P males at 300 and 750 ppm and F_1 males at 750 ppm had reduced body weight gains. No effects were observed in either males or females administered 120 ppm IPBC (Inveresk Research International, Ltd. 1987). Mated female mice, eight in each group, received oral doses of 20, 50, or 125 mg/kg IPBC in corn oil, and eight control mice received the vehicle alone, from days 6–15 post coitum. No signs of maternal toxicity, embryotoxicity, or developmental toxicity were observed in the mice fed 20 and 50 mg/kg. A dose of 125 mg/kg IPBC caused slight maternal toxicity (reduced weight gain from days 10–15), but there was no evidence of embryotoxic or teratogenic effects. The NOAEL was set at 50 mg/kg/day (Henderson 1992).

Mated female Sprague-Dawley rats that received IPBC by gavage were also examined for reproductive effects. Groups of 28, 33, and 30 rats were given 20, 50, and 125 mg/kg/day from days 6–15 of gestation, respectively, then were necropsied. No intergroup differences were observed, either in clinical condition or in necropsy findings. Slight maternal toxicity (reduced body weight) occurred at the high dose at days

6–10, but no other effects were noted. Doses of 20 and 50 mg/kg did not cause reproductive toxicity (Henderson 1992).

Dietary administration of 120, 300, and 750 ppm IPBC to groups of 25 male and female rats per generation (P and F_1) had no effect on fertility or general reproductive performance in either generation. After a 14-week premating treatment period, the parental rats were mated and the offspring kept until weaned. Slight toxicity was observed in P males in the intermediate and high-dose groups, which had reduced body weight gain and reduced feed consumption before mating. F_1 males given 750 ppm also had similar signs during the premating period. No evidence of toxicity was observed in rats fed 120 ppm. Postnatal development of offspring was not affected during the lactation period, but the live birth index was slightly lower in both generations at the highest dose (Henderson 1992).

Groups of 35 pregnant Crl:NMRI Br mice were administered 20, 50, or 125 mg/kg doses of IPBC by gavage. Mice were dosed once daily with 2.0, 5.0, or 12.5 mg/kg IPBC in corn oil on days 6–15 of gestation to give a dose volume of 10 ml/kg/day. There was no positive control. On day 18 of gestation, all mice were killed for necropsy. The results of maternal and fetal examinations are summarized in Table 3. No significant differences were noted between the negative control (0 mg/kg) and the other groups. No treatment-related effects on clinical condition and necropsy findings were observed. IPBC dosing also had no effects on maternal body weight gain or feed consumption, incidence of pregnancy, pre- or postimplantation loss, or the number, weight, or sex distribution of fetuses. Additionally, the incidence of malformations did not change as a result of the study (Hazleton Laboratories, Deutschland 1988a; Henderson 1992).

Pregnant Sprague-Dawley rats were tested in a similar study. Group 1 (28 rats) received 20 mg/kg IPBC in corn oil, Group 2 (33 rats) was

Table 3. Reproductive and developmental toxicity results—mice

Dose level	0 mg/kg	20 mg/kg	50 mg/kg	125 mg/kg
Maternal parameters				
No. of corpora lutea	303	346	354	348
No. of implantations	291	305	311	295
No. of resorptions	43	22	15	28
No. aborting	0	0	0	0
Fetal parameters				
No. of live fetuses	248	82	297	268
No. of dead or resorbed fetuses	43	23	15	29
No. of fetal anomalies	3	3	5	3

Table 4. Reproductive and developmental toxicity results—rats

Dose level	0 mg/kg	20 mg/kg	50 mg/kg	125 mg/kg
Maternal parameters				
No. of corpora lutea	313	331	309	294
No. of implantations	240	276	240	269
No. of resorptions	8	14	6	12
No. aborting	0	0	0	0
Fetal parameters				
No. of live fetuses	232	261	232	256
No. of dead or resorbed fetuses	8	15	8	13
No. of fetal anomalies	1	0	1	2

administered 50 mg/kg, and Group 3 (30 rats) 124 mg/kg. The three groups received 2.0, 5.0, or 12.5 mg/ml, respectively, and all were given a dose volume of 10 mg/ml/day. All rats were administered one dose per day on days 6–15 of gestation, then sacrificed at day 20 for necropsy. Table 4 is a summary of the results of the maternal and fetal examinations. Incidence of malformations and skeletal variations in both the negative control and dosed groups were observed to be comparable. Rats that received the 125 mg/kg dose had a higher incidence of incompletely ossified cranial bones, but this was thought to be temporary or caused by maternal effects (Hazleton Laboratories, Deutschland 1986).

Groups of eight mated female NMRI mice received daily doses of 20, 50, or 125 mg/kg IPBC by gavage from gestational days (gd) 6–15 and were killed for necropsy on gd 18. No treatment-related changes were noted in maternal clinical condition or in necropsy findings. From gd 10–15, body weight gain was slightly reduced at the high dose. There were no effects of IPBC treatment on pregnancy incidence, implantation, postimplantation loss, or the number, weight, and sex distribution of the fetuses. No external malformations were observed in the treated groups. The low and intermediate doses did not induce maternal toxicity, embryotoxicity, or teratogenicity. The high dose produced slight maternal toxicity (reduced weight gain), but was not embryotoxic or teratogenic (Hazleton Laboratories, Deutschland 1988b).

MUTAGENICITY

The *Salmonella typhimurium*/mammalian microsome plate incorporation assay demonstrated that IPBC was not mutagenic with or without metabolic activation. A significant increase in the number of revertant colonies of strains TA1535, TA1537, TA1538, TA100, and TA98 did not occur when 6.3, 18.6, 55.6, 166.7, and 500 μg/plate concentrations

of IPBC were tested when compared to five different positive controls [dimethylsulfoxide (DMSO), methylnitronitrosoguanidine, 9-aminoacridine, 2-nitrofluorene, and 2-aminoanthracene]. The two highest concentrations of IPBC were toxic (Hazleton Biotechnologies Corp. 1984a; Henderson 1992).

In a second study, a micronucleus test was performed in Charles River CD-1 mice. Groups of 15 males and 15 females received a dose of 200, 660, or 2000 mg/kg IPBC in corn oil by oral gavage to give a 10 ml/kg dose quantity. The positive control was cyclophosphamide. Mice were sacrificed at 30, 48, or 72 hours. Doses of 660 and 2000 mg/kg doses proved toxic. No significant increases in the frequency of micronuclei in polychromatic erythrocyte cells were observed; therefore, IPBC was nonclastogenic (Hazleton Biotechnologies Corp. 1984b; Henderson 1992).

A third study utilizing an unscheduled DNA synthesis assay investigated IPBC's genotoxic potential on primary cultures of hepatocytes from adult male Fischer 344 rats. Michler's ketone in ethanol served as the positive control and DMSO the vehicle control. DNA synthesis was determined by silver grain counts in photographic emulsions formed by the cellular uptake of [6-^{3}H]-thymidine. Doses of 3, 4.5, 6, 7.5, 9, 10.5, 12, and 13.5 μg/ml of IPBC did not induce unscheduled DNA synthesis, but treated cultures had decreased viability as the concentration of IPBC was increased (Inveresk Research International, Ltd. 1988b; Henderson 1992). Hepatocytes treated with the highest dose had signs of toxicity, but none of the cultures were positive for genotoxicity (Henderson 1992).

CARCINOGENICITY

In one study on the carcinogenicity of IPBC, groups of 50 male and 50 female Sprague-Dawley rats were given different doses of IPBC in their diet for 104 weeks. The feed, offered ad libitum, was formulated with 20, 40, or 80 mg/kg/day. Blood was drawn and blood counts performed at weeks 53/54, 79, and 104 on control and high-dose rats. Blood samples from 10 rats of each sex and group were also collected. At the end of the 100-week period, all rats were killed for necropsy. Tissues of control and high dose rats, and of the interim deaths in the remaining groups were examined microscopically. Between groups, no significant differences were observed in water consumption, differential blood count, or mortality. Males in all dose groups had a dose response reduction in body weight gain, whereas those that received 80 mg/kg/day dose had slightly lower feed consumption. Females in the 40 and 80 mg/kg/day groups had moderate and marked reductions in body weight gain, respectively. All intermediate and high-dose rats had increased incidences of depressed and raised foci in the stomach, and lesions of the nonglandular stomach and submaxillary salivary gland. No statistical intergroup

differences were found in organ weights. No evidence of carcinogenic potential was detected, and the NOAEL (major structural effects) was set at 20 mg/kg/day for both sexes (Henderson 1992).

CLINICAL ASSESSMENT OF SAFETY

Ippen (1993) classified IPBC as having the lowest possible risk in an allergy test series (nonexistent or extremely rare reactions) that included human sensitization, eczematic skin reactions, contact eczematic potential, cross allergy, and a statistical market evaluation (Ippen 1993; G + G International, Inc. 1995). However, IPBC when moist can cause "moderate skin irritation, primarily to areas of soft, sensitive skin" (G + G International, Inc. 1995).

Primary Skin Irritation

A 4% concentration of a facial cleanser that contained 0.0125% IPBC was tested for the potential to cause skin irritation. Of the 111 panelists, each received an occlusive patch with 0.2 ml of the test material on the volar forearm for 24 hours. Test sites were evaluated 28 and 72 hours after patch application. The observed responses (erythema with or without edema), all of which cleared by 72 hours, were suggestive of mild irritation with some occurrences of moderate irritation. Most subjects, however, did not experience any adverse reactions (Hill Top Research, Inc. 1994e).

5-Day Cumulative Irritation

Undiluted sunscreen lotion containing 0.0125% IPBC applied as an occlusive patch to the upper back of each of 26 subjects for 5 days did not produce significant irritation relative to that caused by a 0.2% sodium lauryl sulfate positive control. Some subjects had positive reactions (minimal to definite erythema), but these reactions were not considered significant (TKL Research, Inc. 1991c). The same formulation did not produce significant irritation when applied in similar manner to the upper backs of 28 children between the ages of 6–12 years old (TKL Research, Inc. 1991d).

21-Day Cumulative Irritation

The cumulative irritation potential of various cosmetic formulations containing IPBC was investigated in the following studies. A dose of

0.2 ml of the test material was applied daily under an occlusive patch applied to the infrascapular region of each subjects' back unless otherwise noted. Patches applied on Friday were not replaced until the following Monday. The positive control in each case was a 0.2% sodium lauryl sulfate. Moisturizing lotion containing 0.0050% (TKL Research, Inc. 1993c), 0.0100% (Ivy Laboratories 1992), or 0.0125% IPBC (TKL Research, Inc. 1993d) had no significant irritation relative to the control when tested on 26, 49, and 26 subjects, respectively. In the case of the 0.0125% lotion, minimal or doubtful erythema or definite erythema were observed in a few cases, sometimes with a papular or papulovesicular response and/or dryness (TKL Research, Inc. 1993d). Moisturizing cream containing 0.0100% IPBC produced insignificant or negligible primary irritation when 0.1 ml was applied to the volar forearm under an occlusive patch. Additionally, the test product was applied twice daily to the entire face (including the forehead and excluding the immediate periorbital areas) of the same volunteers to assess tolerance to the formulation. No adverse reactions were reported, including erythema and scaling. Three subjects, however, experienced the development of new acne lesions (inflammatory papules). Upon examination, it was determined that the outbreak could not be attributed to the test product (Ivy Laboratories 1992). Sunscreen lotion (0.0125% IPBC) did not cause significant irritation relative to a 0.1% sodium lauryl sulfate positive control when applied to the infrascapular region of 27 subjects (TKL Research, Inc. 1994h, 1994i), but one subject had definite erythema (+) throughout the first 16 readings that was accompanied by a papular or papulovesicular response and/or dryness from applications 11–15. On the following application, the subject also had severe damage to the epidermis (oozing, crusting, superficial erosions), and treatment was discontinued. One other subject had definite erythema (+) on applications 12–21 (TKL Research, Inc. 1994i). In similar studies, no significant irritation resulted from the application of the lotion to the forearms of 25 subjects (Ivy Laboratories 1991a), and low irritation potential was determined after application of the lotion to the backs of 28 subjects (TKL Research, Inc. 1994j, 1994k). A facial cleanser (0.0125% IPBC) also did not produce significant irritation when applied as semiocclusive patches to 28 subjects (TKL Research, Inc. 1993e).

4-Week Skin Irritation in Children

When 155 children (3–12 years old) used a full-face, full-body sunscreen (SPF 25) containing 0.0125% IPBC for four consecutive weeks, no adverse effects were observed other than mild sunburn in 34 subjects at the end of the first week (32 on face, 12 on shoulders, 4 on chest, 7 on back, 10 on arms, and 2 on legs) and by four children at the end of the

study (3 on face, 3 on shoulders, 1 on chest, 1 on back, and 1 on arms). The cumulative score for irritation was 82 for week 1 and 9 for week 4. One child reported small, white, pinhead-sized spots on the arms and legs and was diagnosed as having hereditary glandular hyperplasia. In a product experience questionnaire completed by the parents at the end of the 4-week trial, nine subjects reported irritation experiences as burning, stinging, itching, peeling, redness, and/or skin conditions. When examined by a dermatologist, however, these findings were not supported or were diagnosed as being unrelated to the product. Researchers concluded that, because the dermal irritation noted and scored was sunburn erythema and not product related, the sunscreen was safe for its intended use in children (Hazleton Florida 1991).

Human Repeated Insult Patch Test

In a human repeated insult patch test that was an adaptation of the Shelanski and Shelanski method, 170 volunteers aged 18–72 years were treated with a concentration of IPBC determined by the results of two human skin irritation screens. During the first screen, 1.0% and 3.0% IPBC in corn oil produced slight to moderate concentration-dependent irritation after a 24-hour occlusion period. In the second screen, 0.5% to 1.0% solutions of the test substance failed to cause irritation after three repeated applications over 5 days, when each application was followed by 24 hours of a semiocclusive patch (Hill Top Research, Inc. 1994a; Consumer Product Testing Co., Inc. 1995a, 1995b). In the induction test, 0.2 ml of 1.0% IPBC in corn oil was administered three times a week (Monday, Wednesday, and Friday) for three consecutive weeks, then once on the Monday of the 4th week. The challenge concentration and amount applied were the same, but were only administered once. The application site was a 1″ × 1″ nonabraded area on the upper back between the scapulae, and was covered by a semiocclusive patch. The induction test was evaluated 24 or 48 hours after patch removal for Monday and Wednesday or Friday applications, respectively. Following challenge, sites were examined 24 and 48 hours after application of IPBC. No signs of skin sensitization were detected in any of the test panelists (Hill Top Research, Inc. 1994a; Consumer Product Testing Co., Inc. 1995a, 1995b).

The testing details of 32 human repeated insult patch tests on concentrations of 0.01–0.125% IPBC in facial cleaner, sunscreen lotion, sunscreen cream, moisturizing lotion, and moisturizing cream are summarized in Table 5; no evidence of contact sensitization was observed when 0.2 ml was patch tested on the upper arm or infrascapular region of the back. During the induction phase, occlusive patches were applied for 24 hours and the test sites evaluated 48 hours after their application. Following the ninth consecutive application, all subjects were dismissed

Table 5. Human repeated insult patch tests (All tests gave negative results)

Formulation	No. of subjects	Test site	References
		0.0100% IPBC	
Sunscreen lotion	106	Infrascapular	Hill Top Research, Inc. 1994b
Sunscreen lotion	106	Infrascapular	Hill Top Research, Inc. 1994c
Moisturizing cream	106	Infrascapular	TKL Research, Inc. 1992a
Moisturizing cream	95	Upper arm	Hill Top Research, Inc. 1994d
Moisturizing cream	100	Infrascapular	TKL Research, Inc. 1992b
Moisturizing lotion	106	Infrascapular	TKL Research, Inc. 1992a
Moisturizing lotion	96	Upper arm	Harrison Research Laboratories, Inc. 1994
		0.0120% IPBC	
Moisturizing lotion	109	Infrascapular	TKL Research, Inc. 1994b
Moisturizing lotion	109	Infrascapular	TKL Research, Inc. 1994c
		0.0125% IPBC	
Facial cleanser	231	Upper arm	Harrison Research Laboratories, Inc. 1993
Moisturizing cream	100	Infrascapular	TKL Research, Inc. 1992b
Moisturizing lotion	105	Infrascapular	TKL Research, Inc. 1990a
Moisturizing lotion	101	Infrascapular	TKL Research, Inc. 1993a
Sunscreen cream	95	Infrascapular	TKL Research, Inc. 1991a
Sunscreen cream	107	Infrascapular	TKL Research, Inc. 1991b
Sunscreen cream	102	Infrascapular	TKL Research, Inc. 1994d
Sunscreen cream	102	Infrascapular	TKL Research, Inc. 1994e
Sunscreen cream	102	Infrascapular	TKL Research, Inc. 1994f
Sunscreen lotion	95	Infrascapular	TKL Research, Inc. 1991a
Sunscreen lotion	107	Infrascapular	TKL Research, Inc. 1991b
Sunscreen lotion	99	Infrascapular	TKL Research, Inc. 1993b
Sunscreen lotion	201	Upper arm	TKL Research, Inc. 1994a
Sunscreen lotion	208	Infrascapular	TKL Research, Inc. 1994g
		0.0150% IPBC	
Sunscreen cream	97	Upper arm	Harris Laboratories, Inc. 1990c
Sunscreen cream	105	Infrascapular	TKL Research, Inc. 1990a
Sunscreen cream	95	Upper arm	Hill Top Research, Inc. 1991a
Sunscreen lotion	97	Upper arm	Harris Laboratories, Inc. 1990a

(*Continued on next page*)

Table 5. *Human repeated insult patch tests (All tests gave negative results) (Continued.)*

Formulation	No. of subjects	Test site	References
Sunscreen lotion	105	Infrascapular	TKL Research, Inc. 1990a
		0.0375% IPBC	
Moisturizing lotion	99	Infrascapular	TKL Research, Inc. 1990b
		0.0200% IPBC	
Moisturizer (oil/water emulsion)	97	Upper arm	Harris Laboratories, Inc. 1990b
Moisturizer (oil/water emulsion)	95	Upper arm	Hill Top Research, Inc. 1991a
		0.1250% IPBC	
Moisturizing lotion	104	Infrascapular	TKL Research, Inc. 1990c

for a 14-day nontreatment period. Challenge applications were begun during the 6th week of the study, and the test sites were evaluated at 24, 48, 72, and 96 hours (patches were again removed after 24 hours). With each test formulation, a few panelists had erythema, edema, and/or a papular response, but overall, the results were negative.

Human Cross Sensitization

Human subjects (numbering 10 in all) with demonstrated skin sensitivity to Thiuram Mix, a skin contact skin sensitization test formulation containing structurally related dithiocarbamate compounds, were tested with a topical application of 0.2 ml of 0.1% IPBC in soft yellow petrolatum for 24 hours to the upper back (nonabraded skin). The 2 cm × 2 cm test sites were secured with occlusive tape. Application sites were examined at 48 and 96 hours postapplication and compared to a vehicle control patch containing 0.2 ml petrolatum alone. Evaluations of the test areas found no irritation or signs of a cross-sensitization reaction (Inveresk Research International, Ltd. 1995).

Comedogenicity

A 0.1% concentration of IPBC in white (GMS) cream, an aqueous emulsion containing 25% nonionic surfactants and emulsifiers, was tested for comedogenic potential using 12 human subjects between the ages of 18 and 55 who had a history of acne. Application was made to a 4 cm × 4 cm area of nonabraded skin on the upper back, the site was covered by

an occlusive patch, and IPBC was administered three times a week for 4 weeks. The positive control was acetulan. At the end of the exposure period, a follicular biopsy sample was taken and examined. Comedone density was determined stereomicroscopically. A dose of 0.1% IPBC in GMS cream was noncomedogenic in humans under the conditions of this study. Signs of irritation observed were itching or mild to moderately severe erythema. No edema, blistering, discoloration, or scarring were observed (Hill Top Research, Inc. 1995).

Occlusive patches containing 0.2 ml of an undiluted cosmetic formulation were applied three times per week for 4 weeks to the backs of panelists who had been previously screened for their propensity to form microcomedones. The 4-cm^2 patches (test, positive control, negative control) were kept on the application sites for 48 hours, except for those applied on Friday, which remained in place for 72 hours. After a 4-week period, a cyanoacrylate follicular biopsy sample was obtained from each test site and evaluated for microcomedone density. Moisturing gel (Hill Top Research, Inc. 1993a), sunscreen lotion (Hill Top Research, Inc. 1994f), moisturizing cream and lotion (Hill Top Research, Inc. 1992) containing 0.0100% IPBC were all noncomedogenic when tested on 12, 9, and 12 subjects, respectively. In the study testing the moisturizing gel, panelists reported mild to moderately severe itching and mild to moderate erythema (Hill Top Research, Inc. 1993a).

Facial cleanser (Hill Top Research, Inc. 1993b), sunscreen lotion (Hill Top Research, Inc. 1990a, 1994f), moisturizing lotion (Hill Top Research, Inc. 1993c), and sunscreen cream (Hill Top Research, Inc. 1990a) containing 0.0125% IPBC were also noncomedogenic when tested on nine or 11 subjects each. One subject tested with sunscreen lotion experienced mild to moderate erythema (Hill Top Research, Inc. 1993b), and slight increases in microcomedone density were observed in panelists tested with moisturing lotion (Hill Top Research, Inc. 1993c). In a similar study, sunscreen cream (0.00150% IPBC) was noncomedogenic when tested using 12 subjects (Hill Top Research, Inc. 1990b).

Photocontact Allergenicity

In the following studies, the minimal erythema dose (MED) for each subject was determined during a pretesting phase by exposing one side of the midback to a series of exposures to a xenon arc solar simulator in 25% increments. The MED is the time of exposure necessary to produce a minimally visible erythema at 20–24 hours after exposure. Occlusive patches containing 0.2 ml (unless otherwise noted) of the undiluted test formulation were applied to the lower back of each subject for 24 hours (induction phase). Once the patches were removed, the test sites were exposed to three MEDs. This sequence was repeated

twice weekly for 3 weeks, with a 48-hour respite between exposures. Ten days after the last induction exposure, subjects underwent the challenge phase. Patches were applied to untreated skin to the opposite side of the lower back for 24 hours, removed, and the sites irradiated with 4 J/cm^2 UVA. A duplicate set of patches served as an unexposed treated control (Ivy Laboratories 1993a). Sunscreen lotion (Ivy Laboratories 1993b), moisturizing cream, and moisturizing lotion (TKL Research, Inc. 1992c) containing 0.0100% IPBC possessed no photocontact allergenic potential when each was tested on 26 subjects.

The following formulations containing 0.0125% IPBC, moisturizing lotion (Ivy Laboratories 1993a), tested on 25 and 26 subjects each; sunscreen cream (Ivy Laboratories 1991b, 1994a) tested on 25 and 26 subjects; and sunscreen lotion tested on 26 and 27 subjects (Ivy Laboratories 1991b, 1994b), did not possess detectable photocontact allergenic potential. When a dose of 10 μl/cm^2 of moisturizing lotion (Ivy Laboratories 1990a), sunscreen cream, or sunscreen lotion (Ivy Laboratories 1991b) containing 0.0125% IPBC was applied to 26 subjects, the same results were observed. Similarly, when 25 subjects each were tested with sunscreen lotion (Ivy Laboratories 1990b) or sunscreen cream (Ivy Laboratories 1990c) containing 0.0150% IPBC, or moisturizing lotion containing 0.1250% IPBC (Ivy Laboratories 1990d), no evidence of photocontact allergenicity was found.

Phototoxicity

Undiluted moisturizing lotion (containing IPBC at a concentration of 0.0125%) was applied (0.2 ml of test material under occlusive patch) to the lower midback regions of previously screened subjects. None had a medical or dermatologic illness or were sensitive to either sunlight or topical preparations and cosmetics. The irradiated control was a United States Pharmacopeia hydrophilic ointment. Twenty-four hours after application of the patches, the test sites were uncovered and exposed to 20 J/cm^2 of UVA (320–400 nm with a peak of 350 nm). Unirradiated controls were uncovered after exposure to UVA. Test sites were evaluated for phototoxic reactions at the end of exposure and at 24 and 48 hours after irradiation; no evidence of phototoxicity was found (Ivy Laboratories 1993c).

Sunscreen lotion containing 0.001, 0.0125, or 0.0150% IPBC did not possess a detectable phototoxicity potential when doses of 0.2 ml or 50 μl were tested on 10 adult subjects (Ivy Laboratories 1990e, 1991c, 1993d, 1994c). When sunscreen lotion (0.0125% IPBC) was similarly tested on 11 children between the ages of 6–12 years, no phototoxic potential was found (TKL Research, Inc. 1991e).

Moisturizing cream and lotion containing 0.0100, 0.0125, or 0.1250% IPBC did not possess a detectable phototoxic potential when tested on 10–12 adult subjects at the same doses as above (Ivy Laboratories 1990g,

1990h, 1991d, 1993c). Sunscreen creams (0.0125–0.0150% IPBC) had the same results (Ivy Laboratories 1990f, 1991c, 1994d).

SUMMARY

Iodopropynylbutylcarbamate functions as a preservative in cosmetic formulations. In 1996, it was reported to the Food and Drug Administration that IPBC was used in 122 cosmetic formulations. It is approved for use in the European Union.

^{14}C-IPBC was quickly absorbed from the intestinal tract to the bloodstream when administered orally to rats. ^{14}C was detected in the liver, kidneys, skeletal muscle, lungs, heart, skin, and fat tissues after treatment; radioactivity was rapidly eliminated in the urine and exhaled air, and was also detected in the feces. In skin penetration studies using human cadaver skin, $53 \pm 14\%$ of applied ^{14}C-IPBC (0.1%) penetrated the epidermis and papillary dermis and $14 \pm 5\%$ evaporated from the skin surface.

The average acute LD_{50} of IPBC in rats is 1470 mg/kg and researchers assigned a toxicity rating of 3 (moderately toxic) to the compound. In another study, Sprague-Dawley rats given 1000–1500 mg/kg IPBC had soft feces, urine stains, rough coats, and/or slight depression and red stains on the nose and eye areas. Cosmetic formulations containing 0.01–0.0125% IPBC each had an acute oral $LD_{50} > 10{,}000$ mg/kg in rats; 0.0150% IPBC had an acute oral $LD_{50} > 20{,}000$ mg/kg. In 24-hour dermal application studies, IPBC caused erythema and edema of treatment sites in New Zealand white rabbits; the LD_{50} was >2000 mg/kg.

Sprague-Dawley rats administered IPBC as dusts and liquid aerosols had decreased activity, eye closure, and excessive lacrimation. Survivors had labored breathing, gasping, and secretory discharges after exposure. At necropsy, edema, emphysema, and reddened lungs were observed. The average LC_{50} of IPBC was 680 mg/m^3 (dust) or 780 mg/m^3 (liquid aerosol). In a short-term toxicity study, rats fed IPBC for four weeks had decreased weight gain and feed intake; females had increased liver weights and decreased plasma cholinesterase activities. Sprague-Dawley rats used in a 13-week feeding study had transient behavior alteration, increased liver weights, hepatocyte enlargement, stomach lesions, and decreased weight gain following treatment with IPBC. The NOAEL was 20 mg/kg/day.

Other carbamate compounds have inhibited blood acetylcholinesterase activity, resulting in an accumulation of the neurotransmitter, acetylcholine. In a cholinesterase inhibition study, Sprague-Dawley rats were injected with IPBC at doses up to 16 mg/kg. No change in cholinesterase activity was observed.

Several investigators reported that IPBC produces slight dermal irritation in rabbits. IBPC, however, was not a skin sensitizer in guinea pigs. Photosensitization also did not occur in guinea pigs treated with 5% IPBC.

Cosmetic formulations containing 0.5% IPBC caused iritis and conjunctival irritation in the eyes of rabbits. Treatment with 0.1 g IPBC resulted in severe hyperemia, chemosis, discharge, corneal opacity, and conjunctivitis. The iris appeared congested and unreactive to light. When 0.055 g IPBC was instilled, corneal opacity associated with epithelial sloughing, iritis, and conjunctivitis were observed. Cosmetic formulations containing 0.1–0.015% IPBC produced only slight conjunctival redness.

In reproductive and developmental toxicity studies using rats and mice, IPBC had no significant effect on fertility, reproductive performance, or incidence of fetal malformations. Slight maternal toxicity (reduced weight gain) was observed at the highest dose level in one study using Sprague- Dawley rats. In another study also using Sprague-Dawley rats, a higher incidence of incompletely ossified cranial bones was noted in fetuses in the highest dose level group, but was considered related to maternal effects. Reduced maternal weight gain was also observed in studies using mice, but no embryotoxic or teratogenic effects were seen. The NOAEL was 50 mg/kg/day in mice.

IPBC was not mutagenic with or without metabolic activation in the *Salmonella typhimurium*/mammalian microsome plate incorporation assay. A micronucleus test using Charles River CD-1 mice proved IPBC to be nonclastogenic. IPBC also did not induce unscheduled DNA synthesis when primary cultures of Fischer 344 rat hepatocytes were treated. No evidence of carcinogenic potential was found in a 104-week chronic oral toxicity study using Sprague-Dawley rats. The NOAEL of IPBC was 20 mg/kg/day. Dose-related reductions in weight gain were observed, however, along with inflammation of the nonglandular stomach and lesions in the submaxillary salivary gland.

In humans, a 4% cosmetic formulation containing 0.0125% IPBC was mildly irritating when applied under occlusive patches for 24 hours in a primary irritation study. Erythema without edema was observed. Significant irritation was not reported in 5- and 21-day cumulative irritation studies that tested 0.01–0.0125% IPBC in formulation. Concentrations of IPBC ranging from 0.01–0.125% in cosmetic formulations produced no significant irritation or sensitization reactions in human repeated insult patch tests and no evidence of photocontact allergenicity or phototoxicity was found. In other studies, 0.1% IPBC did not cause cross-sensitization reactions in patients with demonstrated sensitivity to related dithiocarbamate compounds.

Cosmetic formulations containing IPBC at concentrations ranging from 0.0015% to 0.1% were tested on human subjects and were non-comedogenic. No data, however, were available on the comedogenicity of higher IPBC concentrations.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel was concerned about the acute inhalation toxicity observed in animal studies with Iodopropynyl Butylcarbamate. The Panel thereby concluded that IPBC should not be included in cosmetic products meant to be aerosolized.

The Panel stated that skin penetration studies using viable skin are preferable to those using cadaver skin. Studies using cadaver skin measure penetration of unmodified compounds only, and do not provide information on the influence of other factors such as skin metabolism. Therefore, studies using viable skin are more useful in assessing the safety of cosmetic ingredients.

The Panel noted that dose-related reductions in body weight gain were observed in a long-term carcinogenicity study using Sprague-Dawley rats, although no evidence of carcinogenic potential was found. Although noting the low degree of sensitization observed in animal studies and in human repeated insult patch tests, the Panel acknowledged the mild dermal irritation potential of this ingredient. Because the highest concentration tested for comedogenicity was 0.1%, the Panel considered that concentration to be the highest for which the available data would support safety.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concludes that iodopropynylbutylcarbamate is safe as a cosmetic ingredient at concentrations $\leq$0.1%. IPBC should not be used in products intended to be aerosolized.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

TO: Lillian Gill, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 29, 2013

SUBJECT: Concentration of Use by FDA Product Category: Iodopropynyl Butylcarbamate

Concentration of Use by FDA Product Category
Iodopropynyl Butylcarbamate

FDA Code†	Product Category*	Maximum Concentration of Use
02D	Other bath preparations	0.015%
03B	Eyeliner	0.009-0.01%
03D	Eye lotion	0.023%
03E	Eye makeup remover	0.018-0.02%
03F	Mascara	0.01%
03G	Other eye makeup preparations	0.009%
04C	Powders (dusting and talcum)	0.02%
05A	Hair conditioners	0.008-0.02%
05B	Hair sprays pump spray	 0.001%
05C	Hair straighteners	0.0008%
05F	Shampoos (noncoloring)	0.00012-0.05%
05G	Tonics, dressings and other hair grooming aids pump spray	0.01-0.02% 0.01%
06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.011%
06G	Hair bleaches	0.0078%
07C	Foundations	0.0025-0.01%
07I	Other makeup preparations	0.009%
08B	Cuticle softeners	0.03%
10A	Bath soaps and detergents	0.02-0.05%
10B	Deodorants (underarm) not spray	 0.0075-0.02%
10E	Other personal cleanliness products	0.015%
11A	Aftershave lotions	0.016%
11D	Preshave lotions (all types)	0.009%
11E	Shaving cream (aerosol, brushless and lather)	0.02%
12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01-0.02%

12C	Face and neck products not spray	0.002-0.05%
12D	Body and hand products not spray	0.002-0.05%
12E	Foot powders and sprays	0.009-0.02%
12F	Moisturizing products not spray	0.015%
12G	Night products not spray	0.01-0.02%
12J	Other skin care preparations wipe product	0.002-0.02% 0.02%
13A	Suntan products not spray	0.01%

†Product category codes used by FDA

Information collected in 2013
Table prepared: July 29, 2013