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Surveillance of dermo-cosmetic products: a global cosmetovigilance system to optimise product development and consumer safety

Background: In the absence of formal marketing authorisation, the manufacturers of cosmetic products are responsible for their compliance with the cosmetic regulations. *Objectives:* To present the key features of a structured, reactive, and rigorous global cosmetovigilance system through practical examples. *Materials & Methods:* During clinical development, adverse reactions are collected formally and analysed by cosmetovigilance experts. After commercialisation, information on reported adverse reactions is sought directly from the consumers. The results of allergological investigations are systematically requested. Pre- and post-marketing cases are analysed along with other sources of information (*e.g.* monitoring of the literature) to detect safety signals per product and per ingredient. A cosmetovigilance index (CVI) is calculated for each formula, based on the number of cases, causality level and number of commercialised units. Updated periodically, it is used to detect signals and select the best tolerated formulas to help formulating new products. *Results:* Examples of safety issues raised during development or after commercialisation, and corresponding corrective actions, are presented. These actions include (but are not limited to) a safety watch to closely monitor adverse reactions, the modification of the formula or a change in the packaging. Cosmetovigilance data also impact future product development, as illustrated by the work done on sunscreens. *Conclusion:* Through the rigorous collection and analysis of adverse reactions during development and after commercialisation, the safety of dermo-cosmetic products can be improved by taking the appropriate corrective actions, monitoring their effectiveness and optimising future product development by focusing on the best tolerated formulas.

Key words: dermato-cosmetics, undesirable effect, signal detection, patch test, allergy, adverse skin reaction

Ensuring the safety of cosmetic products is a regulatory obligation but also a commitment of cosmetic companies. According to the European Regulation on cosmetic products EC No 1223/2009 [1], cosmetic products placed on the market must be safe for human health under normal or reasonably foreseeable conditions of use. Unlike medicines, a balance between risk and benefit cannot be used for cosmetic products to justify a risk to human health [2]. Cosmetic products are not subject to prior authorisation before being placed on the market. Therefore, it is the manufacturer's responsibility to ensure that the product meets the requirements of the cosmetic regulations and that it does not present any risks to human health [3, 4].
To this end, a product safety assessment must be carried out by the manufacturer prior to commercialisation. However, pre-marketing clinical tolerance tests involve a limited number of volunteers. Some adverse reactions can only be detected when the product is marketed and used by a large number of consumers in real-life conditions.

Since 2013, manufacturers of cosmetic products have been required by regulations to report serious adverse reactions to the national competent authorities, in the European Union when Regulation No 1223/2009 came into application [5, 6], as in some other countries in the world (Japan, Israel, Brazil, Turkey). In addition, Australian regulations require the submission of events that were caused by, or may have been caused by, the use or foreseeable misuse of consumer goods or therapeutic goods (considered as cosmetics in the European Union) within two days. In contrast, South Korean regulations ask for periodic reporting of all adverse health effects caused by the use of cosmetics at the end of each semester. Beyond the management of mandatory reports, all the adverse reactions consecutive to the use of cosmetics have to be collected, documented and analysed, thereby setting up a uniform approach to the management of these events.
The monitoring of cosmetic product safety from its preclinical and clinical development [7-10] through to its

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surveillance while on the market is known as cosmetovigilance [11, 12].
The use of cosmetovigilance data is a real challenge for a company developing cosmetic products. Despite rigorous development of formulas, the analysis of clinical development and market surveillance data is necessary to identify ingredients or formulas with tolerance problems through the implementation of a safety signal management process. Cosmetics Europe, the association representing the European cosmetics industry, published guidelines to facilitate the application of the Cosmetic Regulations within companies [13]. However, while the processing of adverse reaction reports is clearly detailed, the process for managing safety signals is still vague.
A robust and global cosmetovigilance system is expected to identify any potential change in a product's safety profile, take preventive or corrective measures if necessary, and disseminate the information for continuous product improvement. We recently proposed a stepwise, standardised approach for the development of safe and well-tolerated dermo-cosmetic products for a paediatric population [14]. The present paper focuses on the key features of a structured, reactive, and rigorous cosmetovigilance system through practical examples of the surveillance of dermo-cosmetic products throughout their lifecycle.

Materials and methods

Since 1999 and before any regulation, Pierre Fabre Laboratories started to build their own Cosmetovigilance Department to enable pre-marketing recording/monitoring and post-marketing surveillance of adverse reactions and serious adverse reactions during the clinical development and worldwide commercialisation of dermo-cosmetic products. A global cosmetovigilance system including early detection of safety signals using multiple data sources, signal rating, adaptative safety monitoring of the product, and corrective actions was put in place. Although the system heavily relies on the post-marketing reports (representing approximately 95% of all cosmetovigilance activities), it also integrates the pre-marketing data to centralise all relevant safety data in one single cosmetovigilance database. The methodology of signal detection and management throughout the product's lifecycle is detailed below.

Pre-marketing recording/monitoring

The formulas are monitored from the beginning of their clinical development, with investigation of each adverse reaction occurring during the different types of clinical studies.
The adverse reactions/serious adverse reactions are collected in a formalised way, as soon as possible after event onset, *via* the clinical experts, the investigators or by direct contact with the volunteers. The adverse reactions are analysed by the internal safety committee, including toxicologists, pharmacists, and dermatologists, and all cases of intolerance are further discussed during the consolidated analyses of safety. If the adverse reactions observed during the clinical studies are considered non-compatible with the nature of the product and the targeted population, the clinical development of the product can be terminated and formulation changes implemented [14].

Post-marketing surveillance

The different steps of post-marketing adverse reaction surveillance are described in Cosmetics Europe Guidelines [13] and are the following: reception, internal recording, collection of information, causality and seriousness assessment, and signal management (*figure 1*).
The main objective of signal management is to identify any potential change in the product safety profile by assessing the product tolerance. All along the process, a constant communication is maintained within the company through regular reviews of cosmetovigilance, position papers, and emails to the relevant company departments (research and development, marketing, executive office).
Information related to the adverse reactions and serious adverse reactions is collected through direct contact with the consumers by phone, email, or letter. An email address and phone number are also available to consumers who would like to report adverse reactions directly to the manufacturer. The information collected (*e.g.* semiology, chronology of the adverse reaction) is analysed by the cosmetovigilance expert. Following this analysis, additional investigations can be proposed (*e.g.* allergological investigations). Pierre Fabre Laboratories provide all ingredients in the formula to conduct the allergological tests, using the concentrations recommended in the Dr Groot's manual [15]. If an ingredient is not coded or if the concentration is not available in the manual, the concentration of the ingredient in the formula is used unless the Pierre Fabre Laboratories internal expert (FGL) advises otherwise. Since 2006, thanks to the collaboration with physicians, results of allergological investigations are systematically requested and most often provided. They are key in the management of contact allergies to a cosmetic product, especially to allow allergen eviction and to detect safety signals per ingredient (*i.e.* emergent allergens).
Other sources of information are considered to detect safety signals per product and per ingredient, such as clinical development data of each class of products, pre- and post-marketing cases, monitoring of the scientific literature, business and scientific background and allergological investigation results. A cosmetovigilance index (CVI) is also calculated for each formula and updated periodically according to the Pierre Fabre worldwide cosmetovigilance system. The CVI calculation is based on the ratio of the number of cases to the number of commercialised units, taking into account the causality level of cases.
The calculation of CVI may evolve to optimise its pertinence, based on the cosmetovigilance data that are collected. Depending on the index value, each formula will be positioned in a cosmetovigilance class (*figure 2*).
Depending on the CVI and class calculation, a safety signal may be issued. An expert review is performed and formulas in Classes III and IV are the subject of a thorough analysis. In most cases, the adverse reactions are non-serious, minor in intensity, and expected considering the nature and known safety profile of cosmetic products. The monitoring approach depends on several criteria such as the date of the

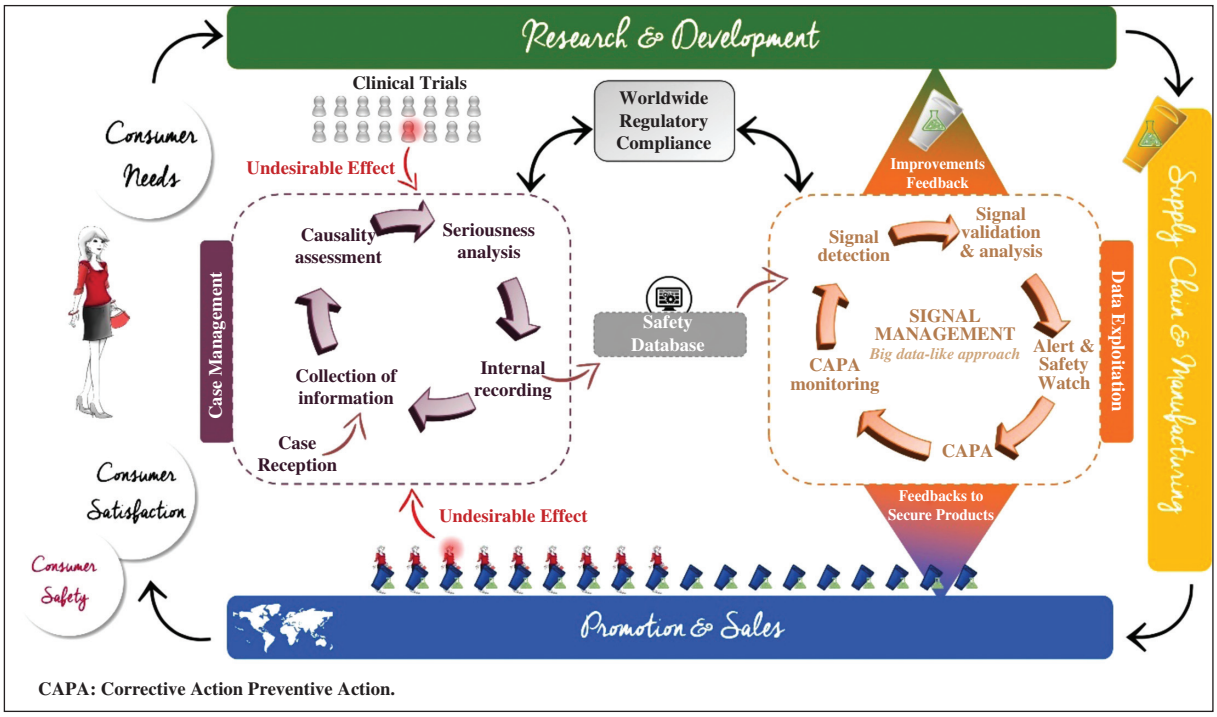

Figure 1. Post-marketing adverse reaction surveillance.

Cosmetovigilance Class	Tolerance Gauge of Cosmetovigilance Index (CVI)
Class IV - Poor Tolerance	IV
Class III - Moderate Tolerance	III
Class II - Good Tolerance	II
Class I - Very Good Tolerance	I

Figure 2. Cosmetovigilance classes and cosmetovigilance index.

The Cosmetovigilance index (CVI) takes into account the number of cases (adverse effects), the causality level and the number of commercialised units.

last report performed and the number of commercialised units on the market.

Formulas in Class IV are automatically placed under safety watch, *i.e.* they are closely monitored at a rate of three cosmetovigilance reports every six months. If the signal is confirmed following these three reports, a cosmetovigilance alert is issued and corrective actions are undertaken, such as changes in the packaging or, exceptionally, product withdrawal (see examples in the results section). The corrective actions are more generally referred to as the CAPA (for corrective action and preventive action). The corrective actions aim at eliminating the causes of non-conformities or other undesirable situations (to prevent recurrence) while the preventive action aims at preventing the occurrence of such non-conformities (based on identified risks). The effectiveness of CAPA is monitored by preparing regular cosmetovigilance reports on the formula.

A product can be removed from safety watch if no safety issue has been raised following the period of close monitoring.

A further step in signal management is the integration of all cosmetovigilance data into one single database (big data approach), which was started by the Pierre Fabre Cosmetovigilance Department in 2016. This project is based on a proven statistical method to perform a new and dynamic signal detection, inspired by pharmacovigilance signal detection methods [16] and applicable to our dermocosmetic portfolio. The objective is to detect signals earlier in order to better protect consumers' health, particularly within vulnerable population groups (sensitive or altered skin, paediatric populations, *etc.*).

Formul'One: another way of using cosmetovigilance data

Formul'One is a project initiated in 2017 to optimise product development by capitalising on well-tolerated formulas. The objective was to select a sample of formulas among 19 product categories (such as sunscreen, anti-aging, atopic skin, body, face or eye contour products) and to provide this list to the Research & Development Department to help formulating new products.

To be eligible, formulas must meet several criteria intended to single out those that are most tolerated among hundreds of available formulas (*figure 3*). To be selected, formulas must:

Not be/have been under safety watch nor under alert.

Have been commercialised for more than 18 months (to have sufficient cosmetovigilance data) and for less than 10 years (to ensure that the cosmetovigilance data were

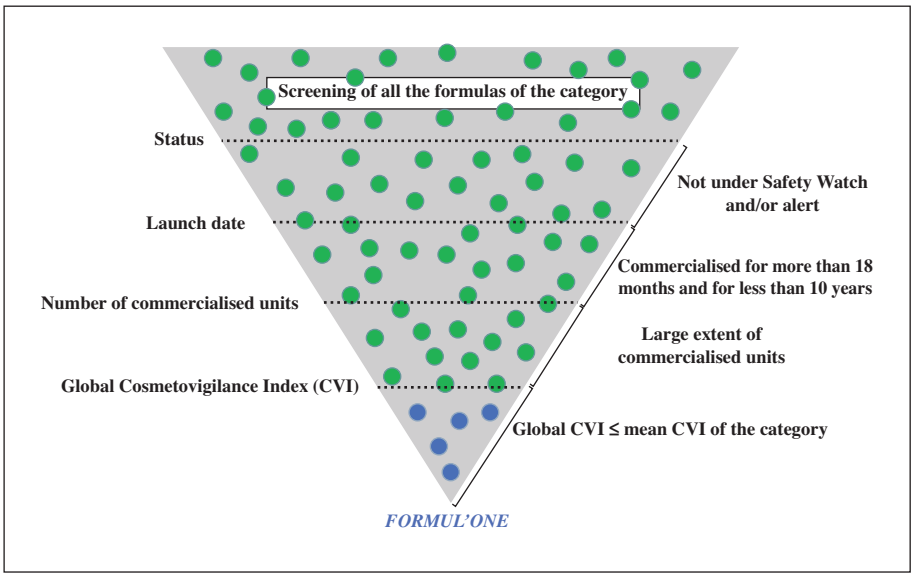

Figure 3. Formul'One project: using cosmetovigilance data to optimise product development by capitalising on well-tolerated formulas.

collected according to the standards of the cosmetovigilance system and in compliance with Regulation No 1223/2009).
Be sold to a large extent.
Have a global CVI ≤ mean CVI of the considered category.
A global CVI is determined for each formula by considering the entire commercialisation period. The mean CVI is the average of global CVIs of all the products belonging to the considered category.
As an example, the Formul'One approach was applied to the sunscreens. The results are presented in the next section.

Results

Example of safety signals detected before commercialisation

As an illustration, we describe the development of a keratolytic dermo-cosmetic product indicated for the management of cradle caps and seborrhoeic dermatitis [17] on face and scalp.
According to our internal guidelines dedicated for the development of this type of dermo-cosmetic product [14], the formula was evaluated through several clinical studies. The different studies, along with the key safety results, are presented in *table 1*.
Initially, a safety use-test under dermatological and ophthalmological control was performed on 30 adults with healthy skin on localised facial areas for two weeks. After analysis of the results and based on the satisfying level of skin and eye compatibility, the formula was tested for two weeks on an adult/teenager target population (*i.e.* seborrhoeic dermatitis, $n = 33$) and finally on infants (*i.e.* cradle caps, $n = 33$) under paediatrician control.
The safety results from external investigators were analysed globally (pooled sample, $n = 96$) by internal clinical, toxicological, and cosmetovigilance experts. Among the 13 subjects (13.5%) who presented a reaction during the clinical program, a total of nine subjects (9.4%) had a stinging sensation (subjective sign) and two subjects (2.1%) were withdrawn for tolerance reason during the paediatric clinical study. These subject withdrawals were decided by the study investigator following the observation of objective signs (erythema, dryness, desquamation) that persisted for a few days. The reactions observed were expected since the product contained lactamide MEA, an ingredient made of lactic acid and monoethanolamine which are both known to be irritating agents. Based on monitoring of the literature, as part of the global cosmetovigilance system, lactic acid was found to be non-irritating to moderately irritating, with no systemic effects reported with dermal application, but potential irritation at the site of application, while ethanolamine was found to be both a skin and eye irritant, with a higher risk of irritation as the contact time with the skin increases.
The occurrence of reactions during clinical development is rare and requires a systematic and global analysis of cosmetovigilance data by experts before launching the product on the market. Following the conclusions of their analysis, the internal experts decided to commercialise the product with close monitoring (*i.e.* safety watch, involving three reports every six months).
After one year of commercialisation and two cosmetovigilance reports, no safety issues have been raised. Only two cases were reported for more than 90,000 commercialised units, and the product was classified as Class I (best class in terms of tolerance, see *figure 2*). A new cosmetovigilance report will be issued after 18 months of commercialisation, in accordance with the safety watch process.

Examples of safety signals detected after commercialisation

Two examples of safety signals detected during the post-marketing period are presented below.

Table 1. Safety results of the clinical studies conducted during the development of a keratolytic dermo-cosmetic product indicated for the management of cradle caps and seborrhoeic dermatitis on face and scalp.

Clinical study design	Population	Safety results	Safety conclusions [0]
In-use tolerance study under dermatological and ophthalmological controls	30 adults with healthy skin Localised areas on the face	2 subjects (6.7%) with a reaction: 2/2 with only subjective signs, with a nature compatible with discomfort [0] *Causality assessment*: the reaction was likely to be related to the product for both subjects.	Very good skin tolerance Excellent eye tolerance
In-use tolerance study under dermatological control	33 adults and teenagers with mild to moderate seborrhoeic dermatitis Localised areas on the face	8 subjects (24.2%) with a reaction: 3 subjects with objective and subjective signs, with a nature compatible with irritation [0] 5 subjects with only subjective signs, with a nature compatible with discomfort [0] *Causality assessment*: the reaction was likely to be related to the product for all 8 subjects.	Good skin tolerance
In-use tolerance study under a paediatrician's control	33 infants with cradle caps on the face and scalp	3 subjects (9.1%) with a reaction: 2 subjects with objective signs, compatible with irritation [0] and leading to the subjects' withdrawal 1 subject with objective signs, compatible with comedogenic reaction *Causality assessment*: the reaction was likely to be related to the product for the 2 subjects who withdrew due to irritation, but not for the subject with the comedogenic reaction.	Good skin tolerance

[1] Safety conclusions were rated using a 5-point scale: excellent, very good, good, moderate, or bad tolerance. [2] Discomfort sensation was defined by the following symptoms (burning sensation, stinging, sensation of warmth, itching, skin tightness, or any other discomfort sensation, provided it was not associated with physical signs such as erythema), intensity (very mild or mild) and duration (less than 30 mins). [3] Cutaneous irritation was defined by the following clinical signs (erythema with or without burning sensation, stinging, tightness, dryness, desquamation) associated with the following topographic symptoms (redness without vesicles and clear and well demarcated edges), observed on the application area.

In 2008, a safety signal on a micellar lotion was issued after four years of commercialisation. A recurrence of allergological investigations that were positive for a surfactant, cleansing and foam-boosting agent of the formula called COCAMIDOPROPYL BETAINE was observed. The allergen was not the ingredient itself, but a synthesis residue, namely dimethylaminopropylamine. The proposed corrective action was to change the formula: in September 2009, a new formula with a cleaning agent was marketed.

The second example concerns the recurrence of misuses of a slimming massage gel. These misuses were collected by the Cosmetovigilance Department. Several subjects did not rinse the product as recommended and experienced severe burns following its application. An alert was issued in October 2017 and the corrective action consisted of adding a pictogram with a shower to the primary packaging of the product. After one year of availability of this new packaging, two cosmetovigilance reports were issued, six months apart, in order to monitor the impact of the corrective action and to control the risk. To date, the effectiveness of the corrective action is still under monitoring, however, the results analysed so far seem to confirm the positive impact on product safety.

Example of the Formul'One project

The work carried out on the sunscreen category allowed to select the most tolerated formulas in the four different galenic forms (creams, emulsion/sprays, lotions and oils), categorised according to their sun protection factor. The formulas selected represent 6.5% of all formulas available in the solar portfolio (*figure 3*).

Discussion

The safety of a dermo-cosmetic product is essentially based on the toxicological risk associated with each ingredient in the formula. This evaluation is challenging due to the specificities of dermo-cosmetic products (in particular regarding exposure and transcutaneous penetration) and the ban on animal testing, forcing the evaluator to use alternative strategies to develop a more comprehensive approach to safety [3].

The cosmetovigilance is fully integrated in the product's lifecycle. From development phases to on-market surveillance, this activity supports and advises the different business partners to ensure that the global safety tolerance is consistent with the worldwide regulations.

The Cosmetovigilance Department put in place by Pierre Fabre Laboratories has been collecting vigilance data for more than 20 years. A specific concept of signal detection was developed to propose a structured, reactive, and rigorous system adapted to dermo-cosmetic products. This system was partly modelled on the best practices of pharmacovigilance and signal detection, which are defined by strict regulations [18-22]. Over the years, the methodology of the global cosmetovigilance system has improved thanks to its increasing maturity, and better availability and quality of the data. With the help of statisticians and powerful information technology (IT), signals are detected earlier.

As an illustration of these efforts, we are working on a multifactorial IT project, named RC360 (RC for Research Code). The objective of this project is to develop an IT to cross-analyse all the data pertaining to a given formula (not only cosmetovigilance data but also data from research and development, commercialisation, *etc*.), to be more precise and efficient in our expertise. Through such initiatives, the Cosmetovigilance Department is able to identify any potential change in a product's safety profile, take preventive or corrective measures if necessary, and provide the information for continuous product improvement.

These improvements allow to focus on formulas and ingredients with the best tolerance for consumers, the "core formulas". Theses formulas will be used as the basis of future products. The cosmetovigilance team is heavily involved in bringing together its expertise on tolerance for the identification of core formulas.

The collection of vigilance data on dermo-cosmetic products relies on the consumers' reports of adverse reactions. In a retrospective study conducted in 1,609 subjects in the Netherlands, 196 (12.2%) cosmetic users reported that they had experienced adverse reactions related to the use of dermo-cosmetic products in the last five years [23]. Other studies conducted in the United Kingdom or in Sweden seem to confirm this incidence [24, 25], while a survey conducted in Italy showed a higher incidence (24.4%) in the 3,474 cosmetic users who participated [26]. However, the true incidence of these reactions is likely to be underestimated [27, 28] because most of the events are mild in intensity; the consumers may therefore decide to stop using the product without necessarily reporting the reaction [4, 29]. Various European surveillance networks engaged in cosmetovigilance have been instrumental in identifying contact allergies [2, 30, 31]. National platforms dedicated to the reporting of adverse reactions are essential to better collect vigilance data [4]. Further efforts should be made to facilitate the report of reactions related to the use of dermo-cosmetic products by physicians and consumers [27, 32, 33]. Pierre Fabre Laboratories regularly hold sessions of information for health care professionals (*e.g*. at conferences) and pharmacists in training (at schools/universities) regarding the reporting of adverse reactions. These professionals are more likely to report moderate to severe cases, with clinical presentation. The key issue remains the under-reporting of mild reactions by consumers.

To date, the global cosmetovigilance system at Pierre Fabre Laboratories is based on quantitative data. A way to extend and refine this analysis could be to add qualitative data, since cultural habits or type of skin vary from one country to another. However, qualitative data imply subjective values, which are more difficult to compare. Once these methodological difficulties are overcome, the cosmetovigilance will be a more powerful aid for business and consumer safety.

In accordance with pharmacovigilance practices, data sharing between companies under the supervision of competent authorities could also drastically expand the capabilities for safety signal analysis and management, thereby helping to protect the consumers' safety.

The systematic collection of adverse reactions and thorough analysis of all safety signals are key to the development of safe cosmetic products. This can only be achieved through transparent and efficient communication with the consumers, by facilitating the report of adverse reactions, encouraging consultation with a healthcare professional if needed, and providing clear usage instructions, labelling, and warnings on the cosmetic products. These actions will improve the consumers' trust and reliability of cosmetovigilance.

Conclusion

The implementation of a structured, reactive, and rigorous cosmetovigilance system not only allows to constantly monitor commercialised products and propose corrective actions if needed, but also optimises future product development by focusing on the best tolerated formulas. ■

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