Annex 1:

CAUSALITY ASSESSMENT OF UNDESIRABLE EFFECTS CAUSED BY COSMETIC PRODUCTS

SUMMARY

A causality assessment method for undesirable effects potentially caused by cosmetic products was developed by a group of experts.

The aim of this reproducible, rational, harmonised and standardised method is to assess cause-and-effect relationships between cosmetic products and given clinical and/or paraclinical effects.

The method is based on six criteria, divided into two groups, which are used to calculate a chronological score and a semiological score.

As a rule, the method must be used separately for each cosmetic product, without taking into account the level of causality of the associated products.

The level of causality is determined using a decision table in which the scores are combined.

The method offers five levels of causality assessment: very likely, likely, not clearly attributable, unlikely and excluded.

Health vigilance systems have two fundamental objectives:

- to record and identify undesirable effects for humans, directly or indirectly caused by a technique, treatment or product;
- to analyse the data collected in order to put in place corrective or preventative measures.

The vigilance process may serve various activities in various fields: improving knowledge, epidemiology, surveillance, signal detection and alerts.

Undesirable effects can occur at random or be linked to specific circumstances or combinations of circumstances or to specific characteristics of each individual.

For a number of reasons, particularly on epidemiological grounds, it can be useful to list already known effects in order to determine their frequency and analyse thoroughly their determinants. By combining their frequency and severity, it is possible to determine the criticality of the undesirable effects, which is one of the central factors in risk management.

However, it is essential to be able to identify undesirable effects irrespective of current scientific knowledge, particularly the scientific knowledge of the reporter and monitor. It is therefore vital not to reject reported undesirable effects on the ground that no causal link can be established.

All healthcare professionals accept that undesirable effects caused by health products cannot be assessed in a purely subjective fashion. The related consequences in terms of health and industrial decisions are significant enough to justify use of an objective and specific diagnostic method.

The aim of such ‘causality assessment methods’ is to estimate the extent of the cause-and-effect relationship between one (or more) health product(s) and the occurrence of an undesirable effect.

As this is a standardised approach, its main advantage is to eliminate any differences of opinion between individual observers [1 to 3]. Such methods are widely applied for most health products in France and are recommended at European level for cosmetic products (Colipa [7], Council of Europe [8]). In France, the first causality assessment method to be used and published was the pharmacovigilance causality method [4, 5], but there was no harmonised French method for cosmetic products.

At the request of AFSSAPS (the French Health Products Safety Agency), a group of experts developed a causality assessment method suited to the specifics of the undesirable effects attributable to use of cosmetic products.

The approach applied to develop this tool established a number of principles:

- Objective: to develop a generic method, applicable to all cosmetic products and all kinds of observed effects.
- Aims of the method: to allow rating of the level of relationship between a suspected cosmetic product and an observed undesirable effect.
- Identification of relevant criteria to establish a cause-and-effect relationship.

- Analysis of these criteria based on the expected outcomes and the weightings to apply to them.
- Combination of these criteria using a decision table.
- Dual validation of the method:
  - theoretical, by checking the relevance of the outcomes obtained;
  - experimental, by using the method in real-life situations.

As is the case for all causality assessment methods [6], implementation of this method:

- is possible only once a minimum amount of information has been collected;
- must be conducted independently for each cosmetic product used before occurrence of the undesirable effect;
- might require specialist medical assessment — this is recommended in complex cases, or if the impact on the user's health is deemed serious.

This search for information should make it possible to identify any other cause, which is a more likely origin of the undesirable effect than the cosmetic product.

The group of experts established a set of intrinsic criteria, involving no data other than those collected on the individual case, for calculating two types of scores:

- a chronological score; and
- a semiological score.

Chronological score

The chronological score is calculated from the information on the time sequence between use of the cosmetic product and occurrence of the symptoms.

The time sequence between use of the cosmetic product and occurrence of the alleged undesirable effect may be:

- compatible, i.e. usual given the reported symptoms;
- only partially compatible, i.e. unusual given the reported symptoms;
- unknown;
- incompatible, whenever the clinical or paraclinical effect occurred before the cosmetic product was used or whenever the period before the observed symptoms appeared is too short.
  If the time sequence is inconsistent, the undesirable effect cannot be attributed to use of the cosmetic product.

Semiological score

The semiological score is calculated from the information on the nature of the undesirable effect and on the results of any specific additional examinations that were performed or of re-exposure to the cosmetic product.

a) Symptomatology

Symptomatology is defined as a set of symptoms, recorded as exhaustively as possible during the case investigation, enabling a diagnosis to be put forward. Absence of diagnosis does not prevent use of this method.

It points to use of a cosmetic product whenever the symptoms observed are appropriate to the nature of the product or to its method of use in terms of location, effect or evolution.

It is otherwise only partially or not at all evocative.

In certain cases, factors that might have contributed to the undesirable effect, i.e. to attenuating or accentuating its clinical expression, may come to light when this information is collected. Although these factors may play a significant role, for the sake of simplification they have not been taken into account in this method.

b) Additional examinations (AE)

Any additional examinations must be reliable and specific to the observed effect and must be performed by specialist physicians.

The results of these examinations are rated as follows:

- AE (+): positive;
- AE (-): negative;
- AE (?): if no examinations were performed or if the results were ambiguous.

c) Re-exposure to the cosmetic product (R)

After the decurrence of clinical signs, there are three possibilities if the effects recur after re-exposure to the cosmetic product, whether accidental or not:

- R (+, positive): the initial symptomatology recurs with the same intensity or with a higher intensity when the user is re-exposed to the product;
- R (?): there is no re-exposure to the product or the conditions of re-exposure are not identical to those of the initial exposure;
- R (-, negative): the effect does not recur when the user is re-exposed to the product.

  For re-exposure to be considered negative, it must occur under similar conditions of use of the cosmetic product (identical product, identical procedure, identical duration, etc.) without causing an identical undesirable effect (identical symptoms and location, identical time sequence before occurrence, etc.).

These scores, combined in a decision table (Table 1) or a decision tree (Table 2), produce five levels of causality: very likely, likely, not clearly attributable, unlikely and excluded.

In this decision table, in principle causality is ‘excluded’ if the time sequence before the effect appears is considered incompatible.

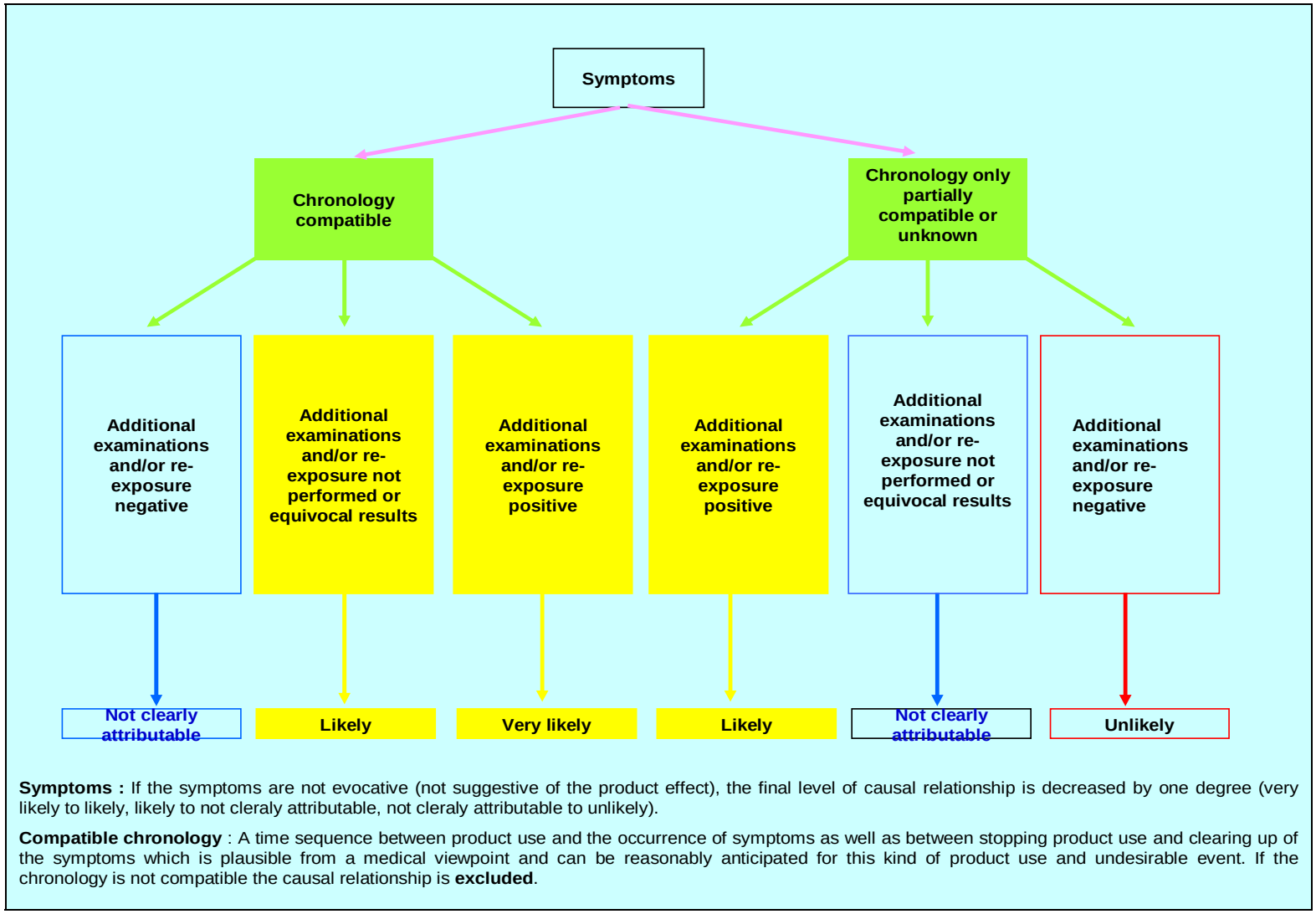
When other aetiologies might account for an undesirable effect observed, these weaken the alleged link between the cosmetic product and the undesirable effect in question and, consequently, the causality is downgraded by one level, but never ‘excluded’.

In any case where another aetiology explaining the undesirable effect observed is demonstrated, medically validated and documented, the alleged link between the relevant cosmetic product and the undesirable effect in question is excluded in this particular case. This other aetiology must be medically validated by a physician specialising in the relevant organ and, whenever possible, be reported in writing.
The excluded cases will be regularly re-assessed as scientific knowledge progresses.

Table 1: Decision table

Symptoms / Time sequence between exposure and occurrence of the symptoms	**EVOCATIVE** of use of the cosmetic product			**ONLY PARTIALLY OR NOT EVOCATIVE** of use of the cosmetic product		
	R and/or AE +	R and/or AE ?	R and/or AE -	R and/or AE +	R and/or AE ?	R and/or AE -
Compatible	Very likely	Likely	Not clearly attributable	Likely	Not clearly attributable	Unlikely
Only partially compatible or Unknown	Likely	Not clearly attributable	Unlikely	Not clearly attributable	Unlikely	Unlikely
Incompatible	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded

Table 2: Decision tree



Symptoms : If the symptoms are not evocative (not suggestive of the product effect), the final level of causal relationship is decreased by one degree (very likely to likely, likely to not cleraly attributable, not cleraly attributable to unlikely).

Compatible chronology : A time sequence between product use and the occurrence of symptoms as well as between stopping product use and clearing up of the symptoms which is plausible from a medical viewpoint and can be reasonably anticipated for this kind of product use and undesirable event. If the chronology is not compatible the causal relationship is **excluded**.

This decision table was used to establish the following definitions:

Causality VERY LIKELY	- the clinical symptoms evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is compatible; - and the specific additional examinations performed are positive and relevant([1]) or the re-exposure to the product is positive([2]).
Causality LIKELY	- the clinical symptoms evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is compatible; - and there are neither any relevant specific additional examinations([1]) nor re-exposure([2]) or otherwise the results of re-exposure or the results of the specific additional examinations performed are ambiguous. Or: - the clinical symptoms evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is only partially compatible or unknown; - and the specific additional examinations performed are positive and relevant([1]) or the re-exposure to the product is positive([2]). Or: - the clinical symptoms only partially evocate or do not evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is compatible; - and the specific additional examinations performed are positive and relevant([1]) or the re-exposure to the product is positive([2]).
Causality NOT CLEARLY ATTRIBUTABLE	- the clinical symptoms evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is compatible; - and the relevant specific additional examinations([1]) or the re-exposure([2]) are negative. Or: - the clinical symptoms evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is only partially compatible or unknown; - and there are neither any relevant specific additional examinations([1]) nor re-exposure([2]) or otherwise the results of re-exposure or the results of the specific additional examinations performed are ambiguous. Or: - the clinical symptoms only partially evocate or do not evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is compatible; - and there are neither any relevant([1]) specific additional examinations nor re-exposure([2]) or otherwise the results of re-exposure or the results of the specific additional examinations performed are ambiguous. Or: - the clinical symptoms only partially evocate or do not evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is only partially compatible or unknown; - and the specific additional examinations performed are positive and relevant([1]) or the re-exposure to the product was positive([2]).

Causality UNLIKELY	- the clinical symptoms evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is only partially compatible or unknown; - and the specific additional examinations([1]) or the re-exposure([2]) to the product are negative. Or: - the clinical symptoms only partially evocate or do not evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is compatible; - and the specific additional examinations([1]) or the re-exposure([2]) to the product are negative. Or: - the clinical symptoms only partially evocate or do not evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is only partially compatible or unknown; - and there are neither any relevant specific additional examinations([1]) nor re-exposure([2]) or otherwise the results of re-exposure or the results of the specific additional examinations performed are ambiguous. Or: - the clinical symptoms only partially evocate or do not evocate use of the product; - the time sequence between use of the product and occurrence of the symptoms is only partially compatible or unknown; - and the specific additional examinations([1]) or the re-exposure([2]) to the product are negative.
Causality EXCLUDED	- the time sequence between use of the product and appearance of the symptoms is incompatible; Or: - another aetiology was demonstrated, medically validated and documented.

([1]) The additional examinations performed to objectify an undesirable effect must be specific and relevant: they must follow an established protocol and allow standardised interpretation. These specific and relevant examinations must be clearly defined.

([2]) Re-exposure may occur in controlled or uncontrolled fashion. The user may either be spontaneously re-exposed to the product which caused the undesirable effect or otherwise be re-exposed to the product following a specific protocol.

A causality assessment method is a key tool for guaranteeing that a uniform and rigorous approach is taken for assessing the strength of links between health products and the occurrence of undesirable effects. This assessment tool is to be used in conjunction with clinical expertise and knowledge of the relevant products, which remain essential.

The method proposed here, which is specific to cosmetic products, supplements the methods commonly used for other health products.

This method must not be considered as definitive per se and must be updated in the light of the experience gained from large-scale use.

References

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