

RECOMMENDATIONS FOR
PREVENTIVE MEASURES
RELATED TO
HYPERSENSITIVITIES
INDUCED BY CHEMICALS



WORLD HEALTH ORGANIZATION
Regional Office for Europe
COPENHAGEN

TARGET 25

HEALTH OF PEOPLE AT WORK

By the year 2000, the health of workers in all Member States should be improved by making work environments more healthy, reducing work-related disease and injury, and promoting the wellbeing of people at work.

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**RECOMMENDATIONS FOR
PREVENTIVE MEASURES RELATED
TO HYPERSENSITIVITIES INDUCED
BY CHEMICALS**

Report on a WHO Consultation

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ABSTRACT

Allergic hypersensitivity, induced by exposure to chemicals, causes such conditions as contact dermatitis and asthma. With the increases in the number of chemicals and the prevalence of hypersensitivity, WHO, the International Programme on Chemical Safety and the Commission of the European Communities held a consultation on the problem. The participants discussed hypersensitivities in general, and allergies of the skin and the respiratory and other systems. They drew conclusions and made recommendations on the problem and ways to prevent it. In particular, the participants called for information programmes for professionals and the public, sentinel surveillance, epidemiological and toxicological research, strategies to control exposure to known allergens, surveillance to estimate the incidence of allergies in countries, and research on predictive testing.

Keywords

HYPERSENSITIVITY
DERMATITIS, CONTACT
RESPIRATORY TRACT DISEASES
FOOD HYPERSENSITIVITY

INTRODUCTION

Exposure to many chemicals results in allergic hypersensitivity, which causes conditions such as contact dermatitis and asthma. Recognizing the growing importance of the problem, in 1982 the WHO Regional Office for Europe and the Commission of the European Communities (CEC), supported by the Government of the Federal Republic of Germany, jointly organized a workshop that evaluated the mechanisms through which chemicals induce allergies and related conditions, related problems in clinical surveillance and epidemiological studies, and possible preventive measures. The participants made specific recommendations on research priorities, the dissemination of information and preventive measures.

Allergic contact dermatitis resulting from exposure to chemicals is a common occupational health problem. Recognition is increasing that chemicals can also induce allergic sensitization in the respiratory tract. The need to assess the problem and to develop preventive measures became evident with the increase in the amount of chemical substances to which a large number of people are exposed.

During the past 10 years, about 10 000 new substances have been marketed in the European Region, and the prevalence and severity of respiratory hypersensitivity have increased. Asthma mortality worldwide has also increased. In 11 of 14 countries, the death rate from asthma was higher in the 1980s than in the 1970s. In six countries, the increase in asthma mortality was over 20%, although the actual numbers were small (range 0.13 to 3.63 per 100 000).

Many substances may cause allergic contact sensitization, but only about 100 chemicals frequently cause allergic dermatitis. Diagnostic tests show that about 15–20% of the population in certain industrialized countries has contact sensitization to chemicals, although disease is much less common.

Recognizing the extent of the problem, the Regional Office, the International Programme on Chemical Safety (IPCS) and CEC, organized the Consultation on Recommendations for Preventive Measures Related to Hypersensitivities Induced by Chemicals with

the support of the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety. The Consultation took place from 14 to 17 December 1992 in the division of the WHO European Centre for Environment and Health in Bilthoven, Netherlands. Experts from nine countries, representatives of CEC, the International Life Science Institute (ILSI) and WHO staff attended. Professor Joseph G. Vos was elected Chairperson and Dr Meryl H. Karol, Rapporteur. The working papers and participants are listed in Annexes 1 and 2, respectively.

The participants were to review progress in scientific knowledge of the prevalence and incidence of clinical disorders related to allergic hypersensitivity, and the causative agents and their mechanisms of action, and to consider diagnostic and predictive testing techniques and other preventive measures. Although the participants focused mainly on allergic hypersensitivity, they also reviewed the disorders that have no immunological basis but are of significant public concern. They gave special emphasis to evaluating the role of man-made environmental chemicals in the development of allergic hypersensitivity, as well as pollutants modulating this response. Finally, a short glossary was developed to reflect the latest developments in the area of allergic hypersensitivities, and to avoid any possible misinterpretation of data. The background papers prepared for the Consultation (Annex 1) will be published.

DISCUSSION

Approach to hypersensitivities

The discussion focused on approaches to understanding people's basic defence systems: physical or chemical reactions, non-specific resistance, and specific immunity, compartmentalized in the skin, respiratory tract, gastrointestinal tract and other body systems. Allergic reactions are classified according to their mechanisms, which may be summarized in terms of initiation, regulation and resulting pathology at the sites where the reactions can occur.

Mechanisms have most often been described in detail for proteins in animal species. Attention focuses on responses in human beings, and responses to compounds with low molecular weight. The discussion mainly emphasized the mechanisms of respiratory and skin allergy, although special attention was paid to the gastrointestinal tract and kidney.

The role of environmental pollution in the development of allergic hypersensitivities is a major cause of concern in the European Region. Although the data show a persistent increase in the prevalence of allergies, causal association with environmental pollution is still under debate. The discussion focused, therefore, on the questions of how to substantiate the necessary epidemiological information related to the population in general and those exposed to pollutants at work. Whether pollutants can alter the allergic inflammatory response should receive high priority in future research.

Further, the participants considered whether pollutants may modulate sensitization, and how they might influence the effector cells in allergic hypersensitivity in sensitized and nonsensitized individuals.

Respiratory allergy

Mechanisms

Chemical respiratory allergy is an immunologically mediated reaction in the respiratory tract that is characterized by a variety of symptoms, including rhinitis and asthma. Sensitization is believed to occur via inhalation, but in theory it might result from exposure via other routes, notably dermal contact.

Respiratory reactions in a previously sensitized individual are elicited after exposure via inhalation. By analogy with protein-induced respiratory allergic reactions, allergic responses to chemicals in the respiratory tract are assumed to be associated with a specific IgE antibody. Other immunological effector mechanisms, however, may play a role of equal or greater importance.

The participants focused on the pathology of allergic hypersensitivity related to the respiratory system. In addition to

general aspects, rhinitis, asthma and hypersensitivity pneumonitis received particular attention. Special emphasis was placed on structure-activity relationships.

Clinical and epidemiological aspects

In addition, the participants reviewed the clinical and epidemiological aspects of respiratory allergic and hypersensitivity responses to chemicals. Rhinitis, asthma and hypersensitivity pneumonitis/allergic alveolitis (HSP/AA) were described. The respiratory effects of outdoor and indoor pollutants were discussed in some detail, including agents such as ozone (O₃), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), total suspended particles (TSP), cigarette smoke and formaldehyde. While not directly acting as chemical allergens, these agents, may have a profound effect on sensitization and allergic respiratory responses to chemicals. Further, the participants reviewed the respiratory effects of occupational exposure to such agents as isocyanate, epoxy resins, colophony, organic and inorganic dusts, and platinum and other metal salts.

The participants tried to evaluate the scope and prevalence of various respiratory sensitivities, utilizing the available published studies and health statistics. Finally, the vexed problem of multiple chemical sensitivity was discussed. The participants concluded that scientific data are lacking to relate the appearance of hypersensitivity to specific agents.

Diagnosis and treatment

The participants reviewed the standard methods of assessing the severity of rhinitis, asthma and HSP/AA, and the appropriate medical therapy to relieve symptoms and prevent long-term respiratory damage. They also discussed the contribution of provocation testing and other, more invasive experimental methods of assessing lung inflammation and damage, with an understanding of their value in the studies. Exposure prevention and the use of anti-inflammatory therapies are crucial in both asthma and HSP/AA. Anti-inflammatory therapies are useful in both diseases, although

damage in the latter syndrome can rarely be fully reversed. Sentinel surveillance has particular diagnostic and investigative value.

Exposure and dose-response relationships

There are two important issues in exposure and dose-response relationships. First, the dose-response relationships of sensitization and of elicitation of respiratory reactions in sensitized individuals may differ widely. Moreover, the concentration required for effective sensitization via different routes may vary. Second, the induction and elicitation of respiratory hypersensitivity and the concentrations of chemical allergens required may vary markedly as a function of a number of factors, including the presence of environmental pollutants (irritant gases) or other response-modifying agents (such as viruses or smoking).

Predictive testing and preventive measures

Respiratory allergy to chemicals is a substantial concern to industry, as large numbers of workers can be exposed. Remarkably, the number of chemicals known to have caused problems appears to be limited. Nevertheless, predictive testing is essential for the development of appropriate environmental health protection. The approaches used include: structure-activity studies, and the assessment of *in vitro* binding of reactive chemicals to proteins and of *in vivo* exposures with measurement of serological endpoints, histopathology and asthmatic episodes (including measurement of hyperresponsiveness of the airways). Some methods rely on endpoints that assume knowledge of the mechanisms of response (such as protein binding and measurement of antibody titre). *In vitro* assessment can provide valuable information, while requiring less use of animals. All methods require validation using positive and negative controls.

In the handling of any chemical, adequate attention should be paid to potential allergenic effects. The participants discussed priorities for the prevention of occupational asthma. They grouped preventive measures into primary, secondary and tertiary activities. Primary prevention focuses on the control of exposures that may cause asthma. Secondary prevention means detection at a

sufficiently early stage to minimize impairment and disability. Tertiary prevention focuses on the provision of appropriate health care for patients with asthma, to avert complications. Specific surveillance programmes, as well as other types of epidemiological investigations, are an important guide to appropriate preventive measures.

Skin allergy

Mechanisms

Extensive research has recently led to unravelling of the basic immunological mechanisms of allergic contact hypersensitivity. It identified the major cell types and mediators involved. How T-cells recognize distinct allergens and how these and other inflammatory cells interact to generate inflammation have begun to be understood. This rapid progress contrasts sharply with the slow progress in unravelling the regulatory mechanisms in cell-mediated immunity, including allergic contact hypersensitivity (ACH). The actions of putative suppressor cells are still heavily disputed. So far, no general method of permanent desensitization has been devised.

Molecules capable of interaction with immune-competent cells, as well as mediators, provide promising targets for anti-inflammatory drugs, some of which have already entered clinical trials.

Clinical and epidemiological aspects

The skin as an organ is involved in a variety of hypersensitivity reactions, whose mechanisms of pathology have not all been clearly established. The most common skin diseases in which allergic or possible allergic reactions play a role comprise: allergic contact dermatitis, including photo-allergic reactions, urticaria, angioneurotic oedema and anaphylaxis, atopic eczema and certain vasculitic diseases (allergic vasculitis, progressive pigmentary purpura).

Allergic contact dermatitis is a major health problem in many industrialized countries. Epidemiological studies of the general population in some European countries show an estimated

prevalence of around 10% for eczema or dermatitis. The figure for contact sensitization is 15–20% because not all sensitized individuals display dermatitis. At any time, it is estimated that 2–4% of the population may have active allergic contact dermatitis. Contact dermatitis accounts for about a third of all cases of occupational disease. Allergic contact dermatitis may have severe consequences. Allergic diseases often start early in life and become chronic, causing years of ill health.

The disease is caused by a T-cell-mediated allergy to a wide variety of substances (such as metals, rubber chemicals, occupational substances, cosmetics, etc.) and manifests in different ways. In some cases, it can be elicited by oral application of the relevant contact allergen (systemic contact dermatitis).

A subgroup of contact dermatitis is due to photosensitization, in which combined exposure to a chemical and ultraviolet (UV) radiation (mostly UVA) elicits sensitization and disease. Immediate hypersensitivity reactions of the skin include urticaria, angioneurotic oedema and anaphylaxis. They are mostly IgE mediated, but some also depend on non-immunological mechanisms (pseudo-allergic reactions). The most common sensitizing agents are drugs and food additives. Epidemiological studies reveal that pseudo-allergic reactions have a prevalence of 1–3% in the general population.

Atopic eczema is a skin disease associated with considerable IgE production. This IgE-mediated hypersensitivity has been found in many patients showing allergic reactions, for example, to aeroallergens or foods. Marked exacerbation of eczematous skin lesions has sometimes been observed after oral provocation with food additives. In many countries, the prevalence of atopic eczema seems to have increased up to 10–15% during the past decades. The reasons for this are unclear; a putative influence of environmental pollutants, such as tobacco smoke, is a focus of research.

Diagnosis and treatment

The discussion confirmed that the diagnosis of allergic diseases comprises the following steps: history, skin tests, *in vitro* tests and provocation tests. Some diagnostic procedures need improvement. Therapeutic strategies comprise allergen avoidance, anti-

inflammatory therapy (with agents acting at different stages of the cascade of the allergic reaction) and optimal skin care.

Drugs found to be effective in preventing severe T-cell-mediated conditions, such as rejection of a vital organ graft, must be shown to be very safe before use in ACH would seem appropriate. To date, measures to prevent ACH, including taking legal action, prohibiting the use of certain materials, or avoiding contact with allergenic materials, are favoured over curative measures. Meanwhile, for difficult-to-avoid allergens, further studies seem warranted of the potential value of tolerance induction before possible sensitization.

Predictive testing

The participants reviewed *in vivo* predictive testing for contact and photocontact allergens.

As to contact allergy tests, the guidelines of the Organisation for Economic Co-operation and Development (OECD) include predictive methods. The main changes in the 1992 version of the guidelines are: recommendation of only two protocols (maximization and Buehler test), a detailed description of the methods, and agreement that a positive result in a mouse screening test (LLNA or MEST) may be definitive evidence of allergenicity, thus reducing any need for additional studies in animals.

Some external factors may influence the induction of sensitization, such as animal husbandry, selection of induction concentrations and reaction assessment. The relevance for humans of results obtained in guinea pigs was discussed.

Human predictive testing has shown overall agreement with the results of animal testing. Technicians need great expertise in performing the tests to exclude misinterpretation. Even the best predictive tests may be unable to indicate allergic contact sensitization in a small population, although it would become evident if a sufficiently large population were examined.

No guidelines yet exist for photocontact allergy tests.

Exposure and dose-response relationships

Many million naturally occurring and man-made chemicals are known. About 1000 to 2000 new chemicals are synthesized and introduced into commerce each year. Chemicals may reach the skin either by direct contact or by airborne exposure. Exposure may take place in occupational or other settings. This distinction has important legal implications but the same allergens often appear both in the domestic and the occupational environments. Many substances have been described as able to cause allergic contact sensitization but only about 100 chemicals or naturally occurring substances commonly cause allergic contact dermatitis.

Exposure to allergens depends on age and can be divided into five different types: in occupational settings, domestic work, hobby and leisure activities, topical medicaments, and cosmetic and personal care products.

The pattern of exposure differs from one geographical area to another, depending on degree of industrialization, and the use and availability of medicaments and naturally occurring substances. Tracing exposure to allergens is crucial for both the primary and secondary prevention of allergic contact sensitization.

Whether the sensitization follows exposure to a chemical depends on many factors, of which the exposure concentration of the chemical is the most important. The induction and eliciting hapten concentrations were tabulated for the most important allergens. In general, the concentration for induction of sensitization is much larger than the minimum eliciting concentration. Genetic factors are important in determining whether a person develops allergic contact sensitization after a given exposure. Other factors may modulate the induction and elicitation of sensitization, including the area of exposure, repetition of exposure, diseases of the skin, age, race and sex.

Preventive measures

Preventing allergic contact sensitization is important because it is a common problem, often causing long-standing contact dermatitis, and thus problems in occupational and social life. The total number sensitized in the population depends on the frequency and intensity

of exposure. The potential is low for exposure in the general environment to chemicals that can induce allergic contact sensitization. Experience has shown that allergic contact sensitization can be prevented by avoiding contact with a known allergen, regulating exposure concentrations or taking preventive measures to protect individuals.

Research in dermatology focuses on the prevention of allergic contact sensitization by the main allergens nickel, chromate, rubber chemicals, preservatives, fragrance materials and acrylates. Establishing preventive programmes for allergic contact sensitization requires:

- (a) information on exposure to chemicals;
- (b) predictive testing;
- (c) diagnostic testing and education;
- (d) epidemiological research and monitoring to set priorities and evaluate the effect of interventions;
- (e) identification of sources of exposure that cause sensitization;
- (f) identification of sensitizing and eliciting concentrations of allergens; and
- (g) research on the induction of tolerance or desensitization.

Allergies affecting other organ systems

Gastrointestinal allergy

Chemicals with low molecular weight rarely, if ever, cause a true allergic reaction in the gastrointestinal tract, as they seldom, if ever, cause primary sensitization via or in it. Most allergic reactions to substances with high molecular weight (including proteins such as milk, eggs and fish) induced via the gut occur during childhood. Sensitization to pollen via the respiratory tract (hay fever) can lead to cross sensitivity to nuts, fruits and vegetables. Contact sensitizers with low molecular weight may induce skin flare reactions in sensitized individuals after ingestion.

Non-allergic reactions to foods exist. Some have known mechanisms, such as a deficiency of the enzyme that digests lactose. Intolerance to food additives has as yet unknown causes. Intolerance reactions have been reported after the ingestion of food additives, such as certain colours, preservatives and antioxidants. While the mechanisms for such reactions are unknown, they are assumed not to be immunological. Most often, symptoms from the skin or respiratory tract are provoked in atopic subjects. The prevalence of food additive intolerance was found to be 1-2% in a group of children in Denmark. In the United Kingdom, a much lower prevalence was found in a group of adults and children who were identified in a different way.

Kidney

Some causes and mechanisms of chemically induced nephropathies in humans were discussed, as chemical sensitivity may occur in the kidney. Few industrial chemicals and environmental pollutants are associated with these nephropathies, but very little research has been done. Knowledge in the renal field would be helpful in understanding the mechanisms of immune-mediated damage in other systems.

CONCLUSIONS

1. People are exposed to many chemicals at work, at home and via the outdoor environment. A limited number of chemicals cause respiratory hypersensitivity, but they are of substantial industrial concern. The prevalence and severity of these problems are increasing. For example, the overall incidence of asthma mortality has been increasing worldwide. While asthma mortality caused by chemicals is not a major public health problem, the worldwide trends may be relevant to the morbidity, loss of work and economic loss resulting from chemical respiratory allergy. Sensitization to chemicals may result from exposure via various routes.

2. Many substances cause allergic contact sensitization, but only about 100 chemicals or naturally occurring substances commonly cause allergic contact dermatitis. In industrialized countries, 15–20% of the population has a positive reaction to chemicals with low molecular weight in diagnostic tests. The most important skin sensitizers are metals (nickel, cobalt and chromate), preservatives (formaldehyde and formaldehyde-releasing substances), isothiazolinones, rubber additives, fragrance materials, plant allergens and acrylate and epoxy derivatives. The most common elicitors of immediate skin reactions are drugs and food additives.
3. Chemicals with low molecular weight do not induce allergic sensitization via the gastrointestinal tract. Contact sensitizers may induce skin flare reactions after ingestion. Certain food additives may cause pseudoallergic reactions, mainly in the skin and respiratory tract. The mechanism of these reactions is not known.
4. Frequency of sensitization is an exposure-related problem, since the induction concentrations for allergic respiratory and contact hypersensitivity are 10–100 times larger than the minimum eliciting concentration.
5. The concentrations of allergens required for induction and elicitation of both respiratory and skin allergy vary markedly as a function of a number of factors that can modulate the response, such as the area exposed, repetition of exposure and the presence of environmental pollutants.
6. Surveillance programmes can give information on the incidence of and trends in allergic disease. This is useful in the setting of priorities for control, evaluation and professional education.
7. Predictive animal testing for allergic assessment has been improved in the past decade. *In vivo* testing indicates only the

potential of a chemical to induce allergy. How genetic and other endogenous factors, such as age, determine susceptibility to sensitization is not fully understood. Although such factors are clearly important for the development of sensitization in individuals, the frequency of sensitization in the population is an exposure-related problem. Hence, the real frequency of allergic sensitization depends on the distribution of the chemical and the exposure of susceptible individuals.

8. During the past ten years, the understanding of some aspects of chemical allergy has significantly increased. Many uncertainties remain, however, and much remains to be learned. The cellular and molecular mechanisms through which chemicals provoke allergic responses require further clarification. Research in this area will pay dividends in allowing the development and use of improved methods for the clinical diagnosis of chemical allergy, and for the prospective identification and characterization of materials that can induce sensitization. New predictive test methods, with emphasis on *in vitro* assays, can minimize the need to use animals and the trauma to which they may be subjected. Research is needed into the genetic and environmental factors that influence the development of chemical allergy.

RECOMMENDATIONS^a

1. Programmes for both health professionals and the public should provide information on exposure to chemicals and allergens. Such programmes should ensure that up-to-date lists of allergenic compounds are available, that products are labelled to indicate the presence of allergenic chemicals and that diagnostic testing is made feasible.

^a The participants considered recommendations 1-6 to have the highest priority.

2. Sentinel surveillance programmes should be used to alert clinicians to potential problems and to prompt early diagnosis, treatment and intervention.
3. Epidemiological and toxicological research should examine the influence of modulating factors (such as pollutants) on the concentrations of chemicals required to induce and elicit respiratory and/or contact allergy.
4. As part of effective primary prevention, strategies and technologies should be developed to control occupational and non-occupational exposures to known allergens and their effectiveness should be evaluated.
5. Surveillance programmes, including epidemiological surveys, should estimate the incidence of and trends in allergic diseases in different countries and population groups, to help to identify risk factors and to determine priorities for public health action.
6. Research is needed to develop and validate predictive tests reflecting the mechanisms of respiratory and dermal allergic hypersensitivity (including photo-allergy). Great attention should be paid to making accurate estimates of dose-response relationships in experimental models. Comparison with data on humans should further validate current predictive methods using experimental animals.
7. As part of secondary prevention, diagnostic reagents and tests should be standardized, and objective, non-invasive methods to evaluate patients with suspected allergy to environmental chemicals should be further developed.
8. Prospective employees and groups with occupational exposure to sensitizing chemicals at work should not be tested, as it will do nothing to prevent sensitization.

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9. The nature of the immunobiological mechanisms that result in the induction and regulation of chemical allergy (through sensitization or tolerance) should be described in more detail. Of particular importance is investigation of how chemical allergens are processed by and presented to the immune system, and the influence of different routes of exposure on the development of sensitization.
 10. The true personal and financial costs of human disease due to environmental chemical allergens should be analysed.
 11. The use of animals in testing should be minimized, and emphasis placed on development of *in vitro* test procedures.
 12. New problems allegedly linked to hypersensitivity should receive rigorous scientific investigation to confirm the existence and nature of syndromes such as multiple chemical sensitivities and pseudoallergic reactions. Research should also facilitate the early detection of new and unknown allergens and chemicals in the environment and diet.

*Annex I***WORKING PAPERS^a**

- ICP/PCS 035/6 Hypersensitivity reactions: definitions,
basic mechanisms and localizations,
by J. Garssen, R.J. Vandebriel
and H. van Loveren
- ICP/PCS 035/7 Mechanisms of skin hypersensitivity to
chemicals,
by R.J. Scheper and B.M.E. von Blomberg
- ICP/PCS 035/8 Predictive testing,
by T. Maurer
- ICP/PCS 035/9 Exposures and dose-response
relationships,
by M.-A. Flyvholm and T. Menné
- ICP/PCS 035/10 Prevention of allergic contact sensitization
to chemicals,
by T. Menné, M.-A. Flyvholm
and H. Maibach
- ICP/PCS 035/11 Gastrointestinal allergy,
by C. Madsen
- ICP/PCS 035/12 Kidney and allergy,
by L. Pelletier, B. Bellon and P. Druet
- ICP/PCS 035/13 Predictive testing,
by M.H. Karol

^a Copies can be obtained from the Toxicology and Food Safety unit, WHO Regional Office for Europe, Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark.

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- ICP/PCS 035/14 Mechanisms of chemical respiratory allergy
by I. Kimber
- ICP/PCS 035/15 Respiratory allergy: clinical and epidemiological aspects,
by L. Rossenwasser
- ICP/PCS 035/16 Respiratory allergy: diagnosis and treatment,
by L. Rossenwasser
- ICP/PCS 035/17 Skin allergy: clinical and epidemiological aspects,
by J. Ring
- ICP/PCS 035/18 Skin allergy: diagnosis and treatment,
by J. Ring
- ICP/PCS 035/19 Preventing occupational asthma,
by K. Venables.

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