

37694

EUR/ICP/PCS 010
3379n
ORIGINAL: ENGLISH

TOXIC OIL SYNDROME AND
EOSINOPHILIA-MYALGIA
SYNDROME

PURSUING PARALLELS IN PATHOGENESIS

Report on a WHO Meeting

Washington, DC
8-10 May 1991

ABSTRACT

A workshop was convened by the Regional Office, in collaboration with the institutions concerned in Spain and the United States, to look into various possibilities for joint investigations of the toxic oil syndrome (TOS) and eosinophilia-myalgia syndrome (EMS). The extremely comprehensive conclusions and recommendations from the meeting point out the similarities and differences between the two syndromes in terms of the clinical aspects, pathology, immunology, epidemiology, chemical toxicology, animal toxicology, and the interdisciplinary lines of investigation and their implications for pathogenesis.

TARGET 22

FOOD SAFETY

Index terms

FOOD POISONING

BRASSICA

EOSINOPHILIA

This report is issued by the Regional Office for Europe in English, French, German and Russian. It may be reproduced, or translated into any other language, provided due acknowledgement is made.

CONTENTS

	<i>Page</i>
Introduction	1
Conclusions	2
Clinical aspects	2
Pathology	4
Immunology	5
Epidemiology	6
Chemical toxicology	8
Animal toxicology	8
Interdisciplinary lines of investigation and implications for pathogenesis	9
Recommendations	9
Clinical aspects	9
Pathology	10
Immunology	11
Epidemiology	12
Chemical toxicology	13
Animal toxicology	15
Interdisciplinary lines of investigation and implications for pathogenesis	16
Annex 1: Participants	18

Introduction

In May 1981, a foodborne disease broke out in epidemic proportions in and around the province of Madrid in Spain. The disease, which came to be called the toxic oil syndrome (TOS), developed in people who consumed denatured rapeseed oil sold illegally as edible oil. TOS affected more than 20 000 people and resulted in several hundred deaths in the first year. Many TOS victims still have symptoms today. TOS was clinically characterized by fever, rash, pneumonitis, myalgia, eosinophilia, and chronic sequelae involving neuromuscular abnormalities, pulmonary hypertension and scleroderma-like skin changes.

In November 1989, a disease outbreak, which came to be called the eosinophilia-myalgia syndrome (EMS), was recognized in the United States. EMS has since been associated with ingestion of the food supplement L-tryptophan, an essential amino acid many people used for insomnia, depression, premenstrual syndrome and less frequently for weight loss and in drug detoxification programmes. Epidemiological and analytical chemical studies have demonstrated that EMS was apparently caused by an impurity (or contaminant) in tablets and capsules containing L-tryptophan. More than 1500 cases have been reported in the United States and 29 people have died, although at least 5000 unreported cases have been estimated. Although EMS has been reported in other countries, the conclusions and recommendations of this report, unless otherwise noted, refer to the syndrome in the United States. Although EMS shares some features with other illnesses, it has much in common with TOS: severe myalgia, intense eosinophilia and multisystem involvement. In addition, EMS appears to have the same potential for long-term sequelae as TOS.

How closely can the parallels in pathogenesis be pursued and what are the implications for common lines of research? How do the essential features of TOS and EMS compare with regard to clinical aspects, pathology, epidemiology, immunology, chemical toxicology and animal toxicology? Are there parallel and converging lines of investigation that can be pursued and what are the implications for pathogenesis?

To answer these questions, a two-and-one-half-day workshop was organized by the WHO Regional Office for Europe, in collaboration with the Spanish Health Research Fund (Fondo de Investigación Sanitaria), US Centers for Disease Control, US Food and Drug Administration, US National Institutes of Health and US National Institute of Mental Health. The workshop was attended by 42 temporary advisers and 4 observers, as well as representatives of the WHO Regional Office for Europe and the WHO Regional Office for the Americas/Pan American Sanitary Bureau.

Conclusions

Clinical aspects

Similarities

1. The organs affected by TOS and EMS are similar: skin, muscles, lungs, nervous system and fasciae. The early constitutional symptoms (such as malaise, fatigue and fever) are also similar.
2. These two syndromes share special features: alopecia, pruritus, xerostomia, pulmonary hypertension and cutaneous papules.
3. Similarities in laboratory results include marked eosinophilia, elevated aldolase with normal creatine phosphokinase and X-ray findings of pulmonary interstitial infiltrates.
4. The two syndromes have evolved, to date, similarly over time. In addition, the differences between TOS and EMS in the early stages tend to disappear in the later stages.
5. Both syndromes show a similar pattern of cutaneous and deep tissue involvement, although the severity may vary.
6. The thrombo-embolic phenomena described in TOS have not been commonly reported in EMS, although unpublished data from

a cohort study conducted in South Carolina suggest a similar prevalence in both syndromes.

Differences

7. Early and often severe lung involvement is virtually universal in TOS but is less prevalent and/or less severe in EMS.
8. The early elevation of immunoglobulin E (IgE) levels in about 50% of TOS cases is generally not seen in EMS cases.
9. The two syndromes affected different populations. This reflects different exposure patterns to the toxic agents, particularly in relation to socioeconomic class, gender and age.
10. The hyperglycaemia and elevated levels of tryglyceride found in the intermediate stage of TOS have not been reported in EMS.

Areas requiring clarification

11. The presence of consistent markers for or definable determinants of susceptibility to the syndrome or its severity needs to be clarified for TOS and EMS. Possible areas of interest are immunogenetics, especially as a potential risk factor for the chronic phase of TOS and EMS, gender and other host factors.
12. The striking weight loss reported in the late phase of TOS needs to be further clarified.
13. Whether TOS and EMS represent a common expression of the same final pathogenic pathway is still unclear.
14. The vague cognitive changes in the late phase of EMS have been difficult to evaluate.
15. Late diagnosis of EMS is difficult. At present the syndrome is defined by a range of symptoms related to known exposure to L-tryptophan. Criteria less stringent than the surveillance definition

lance definition of EMS should be considered in clinical diagnosis and further studies.

Problems with data

16. A comparison of data on the two syndromes is complicated by the following problems:

- somewhat different descriptive terms and standards are used in Spain and the United States to report clinical findings;
- tests now available to study EMS were not available to study TOS ten years ago; and
- differences in the medical care delivery systems in Spain and the United States could affect the interpretation and comparison of the data.

17. National surveillance data on EMS do not contain information on the differing prevalence of specific manifestations of this syndrome over time.

18. Population-based data are incomplete on EMS and, to some extent, for TOS. For example, because of the high specificity of the original surveillance criteria for EMS and because of significant underreporting, all cases of EMS in the United States have not been identified.

Pathology

1. The syndromes have major similarities: vascular changes, pulmonary changes, skin pathology, skeletal muscular lesions, peripheral nerve changes and cardiac abnormalities.

2. The pathological lesions in TOS, however, are much more severe than in EMS, which may indicate that the etiological agent in TOS was more potent or that its action was more extensive and/or intensive than that of EMS.

3. Over time and with further examination, the more chronic changes seen in TOS may be found in EMS.

4. The volume and type of material available for pathological study are currently much greater for TOS than for EMS. This difference is related to the relative size of the epidemics, the distribution of affected people, the greater availability of autopsy material for TOS and the longer period of observation of TOS patients.

Immunology

1. Two significant points of similarity were noted:

- eosinophilia was a prominent component in both syndromes; and
- blood levels of eosinophil granule major basic proteins were elevated in both syndromes.

2. The following important differences were reported:

- IgE levels were elevated early in the development of TOS but not in EMS;
- several types of autoantibodies were common in TOS but an elevated prevalence has not been reported in EMS;
- basophils were decreased in TOS but not in EMS;
- a modest elevation of complement components was reported in some TOS patients but not in EMS patients;
- decreased numbers of CD8⁺ T-cells were found in TOS patients but have not been reported in EMS patients; and
- a possible human leucocyte antigen predisposition was described in late manifestations of TOS but comparable data on EMS are not available.

Epidemiology

1. Epidemiological studies have successfully identified the vehicles of the etiological agents for both TOS and EMS. The etiologic agent for TOS was contained in rapeseed oil denatured with aniline, subsequently processed and sold for human consumption as food. For EMS, the vehicle was contained in the L-tryptophan produced by one manufacturing company in Japan.

2. Although the vehicles have been identified, epidemiological studies have not clearly identified the specific etiological agent for either syndrome. Nevertheless, correlations between illness and certain aspects of the chemical composition of implicated products have been observed.

The presence of fatty acid anilides (particularly oleoyl anilide) in oil samples collected during the TOS epidemic is strongly associated with the presence of illness in the families from which the oil was taken. However, current epidemiological evidence leaves open the possibility that one or more other aniline-based compounds cause TOS or that the etiological agent was a compound unrelated to aniline that was (or arose from) a contaminant in the aniline added to the oil or that was present in the tanker-trucks used to transport oil from France into Spain.

Studies of case and control tryptophan lots from the implicated company show associations between classification as a case lot and the amounts of certain contaminants present in small quantities. The association of a particular chromatographic peak (peak E or peak 97, now known to correspond to 1,1'-ethylidene-bis-[L-tryptophan] or EBT) and the occurrence of illness is of particular interest. Nevertheless, current epidemiological data are insufficient to confirm EBT as the specific etiologic agent of EMS.

3. TOS cases have been caused by exposure to the etiological agent as long as one year after the onset of the epidemic, indicating that this agent may be relatively chemically stable.

4. Current data most consistently indicate an increased risk for TOS among women (possibly related to more frequent exposure)

but with no particular predisposition by age. For EMS, however, although advancing age appears to increase slightly the risk among people exposed to implicated L-tryptophan, gender does not appear to have an influence.

5. The time course and geographic dispersion of the two epidemics differ. The TOS outbreak was explosive, with many cases occurring over a period of weeks in a relatively small area (the province of Madrid and 13 contiguous provinces), and it was therefore identified almost immediately. EMS cases were dispersed throughout the United States, and, although they were concentrated in the summer and autumn of 1989, they had onset over a period of months. Therefore, the epidemic took several months to identify and isolated cases had occurred some years before the outbreak.

6. TOS cases tended to occur in working-class households, whereas EMS cases tended to occur among people of the middle and upper socioeconomic classes. This contrast reflects the differences in the patterns of consumption of the vehicles of the etiological agents.

7. Almost 2% of the approximately 1500 EMS patients have died to date, a proportion comparable to or perhaps even greater than the number of deaths occurring during an equivalent period after the onset of the TOS outbreak. Thus, although early pulmonary involvement is less florid in EMS than in TOS, EMS cannot necessarily be regarded as milder.

8. EMS is not unique to the United States. Cases have occurred in Germany (approximately 100 cases reported), Canada (12 cases), the United Kingdom (11 cases) and other countries.

9. For both syndromes, except in specific cohorts identified by exposure, calculation of overall attack rates is complicated by the absence of clear information on how many people actually consumed the contaminated products and were therefore at risk.

Chemical toxicology

1. Both the L-tryptophan-containing products associated with EMS and the oil associated with TOS contain a variety of chemical impurities. However, in both instances, the best markers of the case-associated product are aromatic amine derivatives. In EMS, it is 1,1'-ethylidene-bis-[L-tryptophan], also referred to as the di-tryptophan animal of acetaldehyde (DTAA), peak E or peak 97; in TOS, these are aniline-related products such as fatty acid anilides.

2. Whether these aromatic amine derivatives cause the respective syndromes is not known. This can only be shown by an appropriate animal model or bioassay. Therefore, researchers are still uncertain whether they should be looking for etiological agents of similar (or identical) chemical structure or of very different structure.

3. Different chemicals have produced some of the clinical symptoms seen in EMS and TOS, but no known chemical or chemical class has produced the same overall pattern of symptoms.

4. Bacitracin has been found in selected L-tryptophan samples. EMS-type symptoms have not been seen after oral administration of bacitracin to humans, but the possible etiological role of modified bacitracin-type compounds should not be ruled out.

Animal toxicology

1. An animal model of TOS has not been identified despite extensive studies in a number of animal systems.

2. Current studies of TOS focus on simulating the denaturation of rapeseed oil with 2% aniline in attempts to mimic or reproduce the refining processes that produced the toxic oil responsible for TOS. The products will be extensively fractionated and various components tested in bioassay systems. These studies may be a better approach than the extensive use of available "toxic" and control oils and other oils with an uncertain relationship to TOS.

3. The Lewis rat may be useful in studying effects of the L-tryptophan samples implicated in EMS and may also be of value in studies of TOS.

Interdisciplinary lines of investigation and implications for pathogenesis

1. The specific etiological agent(s) of TOS and EMS have not yet been fully established.
2. The pathogenic mechanisms of TOS are complex and probably resemble those described in the literature for similar inflammatory, vascular and fibrotic syndromes.
3. EMS probably results from the complex cascade of inflammatory and target cell interactions that evolve over time, including the interactions of cytokines produced by activated cells and the effects of tryptophan metabolites secondarily enhanced during inflammation.
4. The final common pathogenic pathways may be similar in the two syndromes.

Recommendations

Clinical aspects

1. Systematic population-based studies of both syndromes should be encouraged to define the full spectrum of these syndromes and the course of EMS in areas where current case ascertainment has been most intense.
2. Studies should be conducted of both TOS and EMS to determine susceptibility factors for the chronic phase of each syndrome

such as immunogenetic determinants, gender and other host factors.

3. Long-term follow-up of previously identified cases and cohorts of both TOS and EMS should be continued. Diagnostic methods should be developed and validated for later manifestations.
4. The causes of death in TOS and EMS should be compared.
5. Studies should be conducted to determine more clearly whether cognitive changes occur in EMS, to enable more accurate diagnosis and follow-up of this component of the syndrome.
6. To standardize the descriptions of the clinical findings of both syndromes, an international team of physicians should be assembled to collaborate in examining the people affected by TOS or EMS.
7. Efforts should be continued to develop specific diagnostic tools for both TOS and EMS.

Pathology

1. Lesions of the liver, pancreas, breast, salivary glands, central nervous system and gastrointestinal tract have been described in TOS and should be sought in EMS.
2. To enable a more comprehensive comparison with pathological material for TOS, pathological material for EMS should be collected more systematically. Comprehensive histopathological examination should be performed on autopsy material for EMS.
3. Comparative studies of specific organs should be carried out on both syndromes using current immunopathological techniques.
4. New, powerful experimental tools, such as *in situ* hybridization and polymerase chain reaction, should be used to detect any critical

cytokines potentially involved in the pathogenesis of both syndromes.

Immunology

General goals

1. Although several differences between TOS and EMS have been noted, these criteria should be carefully re-examined using preserved TOS specimens wherever possible. Comparable data on EMS are not yet available in some instances.

2. New types of data are needed to determine whether TOS and EMS share immunopathogenic mechanisms. Therefore, the following action should be taken:

- compare the various immunological changes in TOS and EMS;
- distinguish the early and late phases of manifestations and mechanisms for both syndromes;
- search for mediators and effectors of each phase of each syndrome; and
- ultimately, identify the etiological agent in each syndrome.

Specific procedures

3. The abnormal immunological parameters (both humoral and cellular) noted in TOS should be measured over the course of EMS.

4. Levels of appropriate cytokines (such as granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), IL-3, IL-4 and IL-5) should be measured using the well preserved TOS serum specimens. At present, measuring IL-4 levels in blood is difficult.

5. Using fixed sections of tissues available from patients with TOS or EMS, a search should be made with RNA probes for cytokine-producing cells in inflammatory infiltrates.
6. IgE levels in serum samples taken early in EMS should be measured.
7. Production of eosinophil survival factor(s) induced by oil or fractions thereof associated with TOS cases should be measured, as it has in EMS.

Epidemiology

1. For both epidemics, additional information on etiology can probably be gained from further toxico-epidemiological studies that systematically compare chemical analytic measurements and related information corresponding to specific case and control containers or lots of the vehicles of the etiological agents. For TOS, such analyses should centre around derivatives of aniline or of other compounds that may be found to have contaminated the oil. For EMS, the possible agents can be identified by chemical analysis of implicated L-tryptophan lots.
2. Although both epidemics present logistical and methodological difficulties, the systematic collection of information on the long-term evolution of the syndromes should be continued and improved. These efforts should include collecting of data on possible late sequelae of EMS and TOS (such as cardiac arrhythmia, increased incidence of atherosclerotic vascular disease, pulmonary hypertension, various types of cancer and changes in mental state).
3. The mortality of patients affected by each syndrome should be followed up. The overall mortality should be compared with that expected based on age- and sex-specific mortality rates in the population at large. Studies should include analysis designed to detect excess mortality by specific causes of death.

4. As EMS and TOS may represent two specific instances of a spectrum of related diseases involving eosinophilia, countries should consider implementing surveillance for eosinophilia. Such surveillance could be conducted from selected sentinel points to make it more economical.
5. The possible relationship between environmental factors other than L-tryptophan and toxic oil and known diseases involving eosinophilia (such as the hypereosinophilic syndrome) should be investigated.
6. Follow-up of EMS in the United States should concentrate on areas where case-finding has been particularly intense and on certain cohorts for which exposure data are especially good.
7. Studies to determine whether a particular human leucocyte antigen haplotype is associated with an increased risk of the chronic phase of EMS should be completed.
8. Cases of EMS or EMS-like illness in people without a history of tryptophan ingestion should be followed up to determine whether any other exposure might account for the illness.
9. Patients being administered L-5-hydroxytryptophan, either in controlled trials or in any other context, should be monitored carefully for the development of eosinophilia or any other signs or symptoms of EMS or TOS.

Chemical toxicology

1. The chemical analysis for the etiological agent(s) in EMS and TOS should continue.
2. A network for communication among researchers involved in the chemical elucidation of EMS and TOS should be set up and maintained.

3. In the TOS investigation, further attempts should be made to learn what chemicals and products the tanker-trucks that hauled the implicated oil had previously transported.
4. In the EMS investigation, the particular L-tryptophan manufacturer implicated should be encouraged to provide additional batches of L-tryptophan produced under various operating conditions, along with some of the cultures of the bacterial strains, to appropriate investigators.
5. Detailed flow charts of the production and purification of L-tryptophan (both during and before the manufacture of case-associated L-tryptophan) and of the production and purification of TOS-related oils should be developed. Any processes that may lead to similar by-products (such as anthranilic acid derivatives) should be scrutinized.
6. Samples of lysine, nicotinic acid and ascorbic acid (vitamin C) allegedly linked to EMS should be chemically analysed for compounds of similar structure to those found in case-associated, L-tryptophan-containing products.
7. Analysis for 3-phenylamino-1,2-propanediol and its derivatives in TOS-associated oil and control oil should be considered.
8. The case-associated, L-tryptophan-containing materials and toxic oil samples, along with controls, should be fractionated and closely examined by a combination of suitable animal and *in vitro* bioassay tests and chemical analysis.
9. The literature on other aromatic amine compounds prescribed or regularly ingested should be reviewed to determine whether similar cases of illness have occurred.

Animal toxicology

1. Animal studies of EMS should be extended to other species, including various strains of mice, other strains of rats, dogs and primates. The metabolism of suspected etiological compounds of both EMS and TOS should be studied in whole animal systems or, if appropriate, *in vitro* systems.

2. In view of the importance of developing an animal model for both TOS and EMS, the following should be given high priority.
 - (a) Current experiments on EMS with the Lewis rat should be continued, refined and validated. This potential animal model should be examined very carefully, and studies should fully evaluate all lesions related to treatment with contaminated samples of L-tryptophan. The cell types involved in such lesions should also be characterized.

 - (b) Use of the Lewis rat for TOS studies should be explored, with special emphasis on the use of TOS-related case oil and known chemical constituents of these oils.

 - (c) As work progresses, the relationships between the results obtained using the Lewis rat and *in vitro* bioassay systems must be qualitatively and quantitatively examined.

 - (d) The products obtained from the simulated manufacturing and refining processes should be examined in both *in vivo* and *in vitro* test systems as sufficient quantities of the compounds become available.

 - (e) Every effort should be made to duplicate the strains of seed and the processing conditions used to produce the crude rape-seed oil that were ultimately implicated in the production of

toxic oil associated with TOS. Possible contributions to toxicity from glucosinolates and indolylglucosinolates or other components should be considered in this work.

Interdisciplinary lines of investigation and implications for pathogenesis

Investigators need to determine whether the etiological agents in TOS and EMS are similar or unrelated. The range of potential etiological agents should be defined by testing a variety of epidemiologically implicated and chemically related agents in both *in vivo* and *in vitro* systems.

The pathogenesis of the syndromes should be compared by defining the range and pattern of stimulating cytokines and the activation products of the target cells involved. Assays should be carried out on serum, plasma, and preserved cells and tissue sections. Analytic techniques should include biochemical analysis, radioimmunoassay, northern analysis, *in situ* hybridization, histochemistry and light and electron microscopy, as appropriate.

1. Additional common potential etiological agents in TOS and EMS should be compared in animal systems and in *in vitro* assay systems. These agents should include synthetic precursors and metabolites common to both denatured oils and L-tryptophan such as anthranilic acid and aniline-like compounds. The etiological agent in fog fever, 3-methyl indole, might also be evaluated.
2. The patterns of cytokine factors involved in TOS and EMS should be defined and compared. These should include eosinophil-stimulating cytokines, such as IL-3, IL-5, GM-CSF, interferon alpha and interferon gamma, and fibroblast-stimulating cytokines, such as T-cell growth factor b.
3. Target cells, including lymphocytes, macrophages and fibroblasts, should be examined for activation markers. Cell activation

products (such as collagen types) and eosinophil products, including major basic protein and eosinophil-derived neurotoxin, should be sought in lesions.

4. Target tissues should be examined for additional cells that could contribute to inflammation and fibrosis (mast cells and platelets).

5. Accurate, quantitative and rapid read-out systems to identify induction of any features of the syndromes *in vitro* and *in vivo* should be established. These could include pathological, histochemical, molecular and biochemical methods, depending on the study system being examined.

6. Epidemiological and clinical studies should be directed at determining the pathogenic factors. Epidemiological approaches could be particularly useful in determining potential contributing host factors and the possible contribution of concurrent medication use in patients who ingested less of the implicated L-tryptophan and in determining factors that predispose towards evolution of the syndromes to the chronic phase.

*Annex 1***PARTICIPANTS****Temporary Advisers**

- Dr I. Abaitua-Borda
Fondo de Investigación Sanitaria (FIS), Madrid, Spain
- Dr W.N. Aldridge
4 Stoke Charity Road, Kings Worthy, Hampshire, United Kingdom
- Dr E.E. Back
New York State Department of Health, Bureau of Environment and Occupational Health, Albany, NY, United States of America
- Dr E.A. Belongia
AIDS/STD Prevention Services, Minnesota Department of Health, Minneapolis, MN, United States of America
- Dr J.T. Bernert, Jr.
Division of Environmental Health and Laboratory Sciences, MS F19, Centers for Disease Control, Atlanta, GA, United States of America
- Dr R. Cottrell
Leatherhead Food RA, Leatherhead, United Kingdom
- Dr L. Crofford
Arthritis and Rheumatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Disease, National Institutes of Health, Bethesda, MD, United States of America
- Dr M. Dalakas
Neuromuscular Disease Section, National Institutes of Health, Bethesda, MD, United States of America
- Dr A.G. Engel
Mayo Medical School, Mayo Clinic, Rochester, MN, United States of America
- Dr H. Falk
Environmental Hazards and Health Effects, Centers for Disease Control, Atlanta, GA, United States of America

-
- Dr E. Gelpi
Centro de Investigación y Desarrollo, Departamento de Neuroquímica,
Barcelona, Spain
- Dr G.J. Gleich
Mayo Medical School, Mayo Clinic, Rochester, MN, United States of
America
- Dr W. Glinsmann
Center for Food Safety and Applied Nutrition, Food and Drug Administra-
tion, Washington, DC, United States of America
- Dr R. Goulding
36 Ashley Court, Morpeth Terrace, London, United Kingdom
- Dr P.A. Hertzman
Los Alamos Medical Center, Los Alamos, NM, United States of America
- Dr R. Hill
Environmental Health and Laboratory Sciences, Centers for Disease Con-
trol, Atlanta, GA, United States of America
- Dr Mary L. Kamb
Centers for Disease Control, Atlanta, GA, United States of America
- Dr L.D. Kaufman
Division of Allergy and Rheumatology, Health Sciences Center 16, State
University of New York, Stony Brook, NY, United States of America
- Dr E.M. Kilbourne
Epidemiology Program Office, Centers for Disease Control, Atlanta, GA,
United States of America
- Dr K.C. Klontz
Clinical Assessment, Food and Drug Administration, Washington, DC,
United States of America
- Dr C. Lahoz
Departamento de Inmunología, Clínica de la Concepción, Fundación
Jimenez Dias, Madrid, Spain
- Dr S. Madero Garcia
Hospital "12 de Octubre", Madrid, Spain
- Dr A. Mayeno
Mayo Medical School, Mayo Clinic, Rochester, MN, United States of
America
- Dr T.A. Medsger Jr
Division of Rheumatology & Clinical Immunology, Pittsburgh, PA, United
States of America

- Dr J. Nadal
Hospital General de Cataluña, Barcelona, Spain
- Dr J.J. Navas-Palacios
Hospital Germans Trias y Pujol de Badalona, Barcelona, Spain
- Dr L. Needham
Environmental Health and Laboratory Sciences, Centers for Disease Control, Atlanta, GA, United States of America
- Dr Rossanne M. Philen
Division of Environmental Hazards and Health Effects, Centers for Disease Control, Atlanta, GA, United States of America
- Dr M. Posada de la Paz
Fondo de Investigación Sanitaria (FIS), Madrid, Spain
- Mr L.E. Posey
Division of Environmental Hazards and Health Effects, Centers for Disease Control, Atlanta, GA, United States of America
- Dr Jeanne Rader
Nutrient Toxicity Section, Division of Nutrient, Food and Drug Administration, Washington, DC, United States of America
- Dr. J.J. Gómez Reino
Hospital "12 de Octubre", Madrid, Spain
- Dr F. Pozo Rodrigues
Fondo de Investigación Sanitaria (FIS), Madrid, Spain
- Professor N.R. Rose
Department of Immunology and Infectious Diseases, Johns Hopkins University, School of Public Health, Baltimore, MD, United States of America
- Dr Mercedes Diez Ruiz-Navarro
Fondo de Investigación Sanitaria (FIS), Madrid, Spain
- Dr L.E. Shulman
National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, United States of America
- Dr R. Silver
Department of Medicine, Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC, United States of America
- Dr L. Soldevilla
Fondo de Investigación Sanitaria (FIS), Madrid, Spain

- Dr J. Sphon
Institute of Biophysics, Food and Drug Administration, Washington, DC,
United States of America
- Dr Esther M. Sternberg
National Institute of Arthritis and Musculoskeletal and Skin Diseases,
National Institutes of Health, Bethesda, MD, United States of America
- Dr F. Martinez Tello
Departamento Anatomía Patológica, Hospital "12 de Octubre", Madrid,
Spain
- Dr J. Varga
Scleroderm Center, Thomas Jefferson University, Philadelphia, PA, United
States of America

Observers

- Dr Lisa Carr-Fischer
Clinical Research, Fresenius AG, Oberursel, Germany
- Dr T. Ichikawa
Applied Food Research Division, National Institute of Health and Nutri-
tion, Tokyo, Japan
- Dr Lori A. Love
Center for Food Safety and Applied Nutrition, Food and Drug Administra-
tion, Kensington, MD, United States of America
- Dr K. Ono
Division of Pharmacognosy and Phytochemistry, National Institute of
Hygiene Sciences, Tokyo, Japan

World Health Organization

Regional Office for the Americas/Pan American Sanitary Bureau

- Dr C. Almeida
Veterinary Public Health Programme
- Mr A. Trujillo
Veterinary Public Health Programme

Regional Office for Europe

Dr S. Tarkowski

Director, Environment and Health

Ms Elaine C. Grandjean

Project Administrator, Special Project on Toxic Oil Syndrome

Ms Susana Louro

Secretary, Special Project on Toxic Oil Syndrome