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# Management of an Integrated Project (Sens-it-iv) to Develop *In Vitro* Tests to Assess Sensitisation

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**Summary** — Sens-it-iv is an integrated project, funded by European Commission Framework Programme 6, the overall objective of which is to develop *in vitro* tests and test strategies to be used by the chemical, cosmetic and pharmaceutical industries to assess the risk for potential contact and respiratory sensitisers. Such tests, once formally validated and accepted, will permit the evaluation of the sensitising potential of existing and new chemical entities and the products of the European industries for classification and labelling, as required by the new EU REACH legislation on chemicals, or for the purpose of risk assessment as required by the 7th Amendment to the EU Cosmetics Directive. Sens-it-iv involves 28 partners, representing industries, universities and regulatory bodies, including various institutes in the EU Member States and different competencies, all with the common aim of achieving a final deliverable — increasing the safety of consumer products, whilst reducing animal experimentation. This paper provides an overview of the structure of the project and a detailed description of the organisation of its management.

**Key words:** contact sensitiser, cosmetics testing, replacement alternative, REACH system, respiratory sensitiser, Sens-it-iv.

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## Introduction

Chemicals are able to cause various forms of allergic disease. In an occupational health setting, skin sensitisation resulting in allergic contact dermatitis — and allergic sensitisation of the respiratory tract, associated typically with rhinitis and/or asthma — are most commonly encountered. In both cases, allergic sensitisation is acquired following contact with the inducing chemical allergen under appropriate conditions of exposure. If the sensitised subject is subsequently exposed to the same chemical, an accelerated and more aggressive secondary allergic response to the chemical may be elicited, resulting in a true allergic reaction.

Allergic contact dermatitis is a common occupational and environmental health problem, and many hundreds of chemicals have been shown to have the potential to induce skin sensitisation. Allergic sensitisation of the respiratory tract by chemicals is less common, but is of no less importance, as occupational asthma is associated with significant morbidity, and may even be fatal. In both cases, there is a need to identify and characterise chemicals that have the ability to induce skin and respiratory sensitisation, and to assess accurately the likely risks to human health (1).

Currently, hazard prediction and risk assessment for potential skin sensitisers rely completely on animal testing, while there are no accepted methods for the evaluation of respiratory sensitisers (2). However, the 7th Amendment to the EU Cosmetics Directive, *Directive 76/768/EEC* (3), calls for a complete ban on animal testing for cosmetic ingredients to be implemented at the latest by 11 March 2009; the ban is already in force for cosmetic finished products. Moreover, the new EU legislation on chemicals, the REACH system (4), clearly states that tests on animals should be adopted only as a last resort. Despite these regulatory needs, no accepted *in vitro* methods are currently available for sensitisation. The Sens-it-iv project was created in order to help fill this gap. The overall objective of the project is to develop and optimise an *in vitro* testing strategy that could reduce or replace animal testing for sensitisation. Besides reducing animal experimentation, emphasis will be given to increasing the accuracy of predicting the sensitising potency of chemicals, in order to enhance the safety of consumer products.

Sens-it-iv is the acronym for *Novel Testing Strategies for In Vitro Assessment of Allergens*. The total budget amounts to €14,592,700, of which €10,999,700 is being funded by the European

Commission (EC) within Framework Programme 6 (FP6). The project officially started on 1 October, 2005, and will continue until 30 September, 2010. It involves 28 partners, representing industries, universities and regulatory bodies. An FP6 integrated project brings together different institutes and different competencies in different EU Member States, so its management is very challenging. The coordination includes the involvement of each partner through the assignment of specific responsibilities, training, and establishing trust among the participants, to provide for efficient sharing of information and results.

## FP6 and Sens-it-iv

FP6 has, “as a main goal, the strengthening of the scientific and technological bases of industries, and encourages European international competitiveness, while promoting research activities in support of other EU policies”. Sens-it-iv addresses the specific objectives of the FP6, as clearly indicated under the Thematic Priority, *Life Sciences, Genomics and Biotechnology for Health*, and in particular, the Thematic Area, *New In Vitro Tests to Replace Animal Experimentation*. The project integrates a critical mass of public and private research capacities across Europe, and their expertise and resources, to provide for a real impact in scientific, industrial and

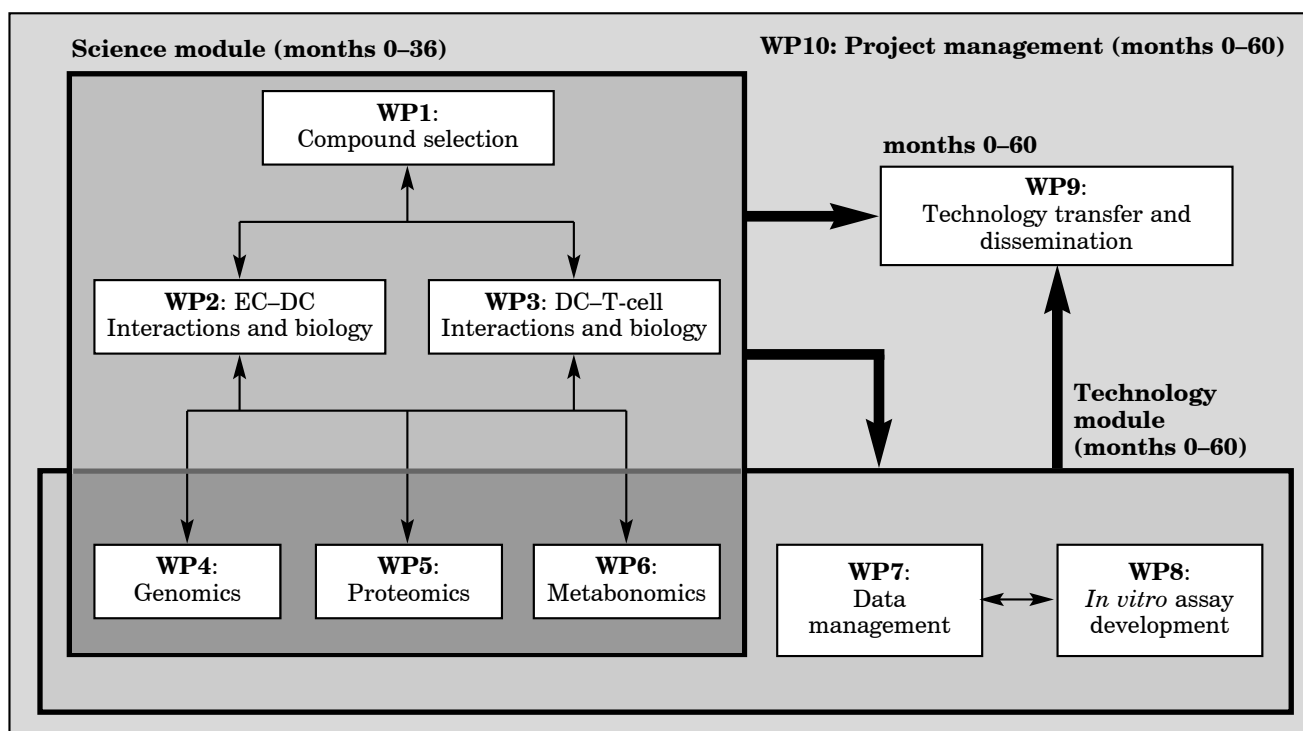
economic terms. The involvement of partners from industries and academia with a recognised expertise in the field, key stakeholders in the field of validation (ECVAM) and in the promotion of alternative methods (Colipa [the European Cosmetic Toiletry and Perfumery Association], ECOPA [the European Consensus-Platform for Alternatives], and IVTIP [the *In Vitro* Testing Industrial Platform]), as well as the early involvement of regulators, guarantees the integration of competencies in seeking to meet the goal of the project.

The management of a project approved within FP6 has to follow precise rules, within which a Consortium with considerable autonomy is established, with a Consortium Agreement in which the relationships and responsibilities of the individual partners are defined in detail. The contract between the EC and the Consortium is not active, unless such a Consortium Agreement has been signed by all the contractors. Furthermore, all activities under FP6 have to be conducted in strict compliance with ethical principles.

## Project Structure

To facilitate its management, the project is structured in modules and work packages (WPs) (Figure 1). The science module (WPs 1–6) aims to provide the scientific foundation and knowledge to the tech-

**Figure 1: The structure of the Sens-it-iv project**



nology module (WPs 4–8) for the design and development of alternative predictive methods. Such methods will be optimised and standardised to meet the criteria for entering the ECVAM prevalidation process (5). Technology transfer and dissemination activities are assured by WP9. Finally, the coordination of the various activities, the training of the project partners, and contact with the European Commission are the major tasks in WP10 (project management).

The science module primarily involves fundamental research, and will be active during the first 3 years of the project. Within this module, WP1 is generating a database of fully-characterised reference chemicals and proteins. As the project proceeds, the information on the chemicals will be expanded with data concerning hapten–protein interactions and metabolic bioactivation. WP2 and WP3 are developing a detailed understanding of the pivotal roles of epithelial cells (ECs), dendritic cells (DCs) and specific T-cells in the induction of contact sensitisation and respiratory sensitisation. Both these WPs are using a selection of the compounds provided by WP1 (the learning set) for the characterisation of the inter-cellular and intra-cellular and molecular mechanisms that are specifically required for the acquisition of sensitisation. The main difference between the two WPs is that WP2 looks from the ECs toward the T-cells, by using T-cell activation primarily as a tool to evaluate the interaction between ECs and DCs. In contrast, WP3 addresses the issue via the T-cell compartment, by using EC–DC interactions to provide an understanding of how potential sensitisers may affect these interactions to result in Th2-mediated responses. Since both WPs involve the same cell types, intensive coordination and training via WP10 is required to assure synergy of the research activities and optimal use of the knowledge acquired. WP4 (genomics), WP5 (proteomics) and WP6 (metabonomics) belong to both the scientific module and the technology module. They provide the analytical tools for the identification of relevant mechanistic pathways and markers of interest for WP2 and WP3, as well as for the characterisation of cells, cell types and cell–cell interactions. In addition, WP5 and WP6 contribute to the understanding of hapten-formation and the metabolic activation of chemicals suspected to be sensitisers.

The aim of technology module is to collect and implement the knowledge acquired by the science module, and it can be considered to be an applied research module. While some of the activities can be initiated early in the project (e.g. data collection by WP7), this module cannot be fully operational in terms of assay development (WP8) unless a minimum critical mass of knowledge is available.

From the onset of the project, relevant properly-evaluated information from each WP (e.g. standard

operational procedures, analytical data, and guidelines) have been transferred to WP7 for incorporation into an inductive database. This database is an easily accessible platform for storing raw data, running specific queries and sharing information among the partners. Eventually, test results collated with other relevant chemo–physical properties will enter a programme built *ad hoc*, which will utilise statistical approaches for a computer-based Intelligent Testing Strategy (ITS).

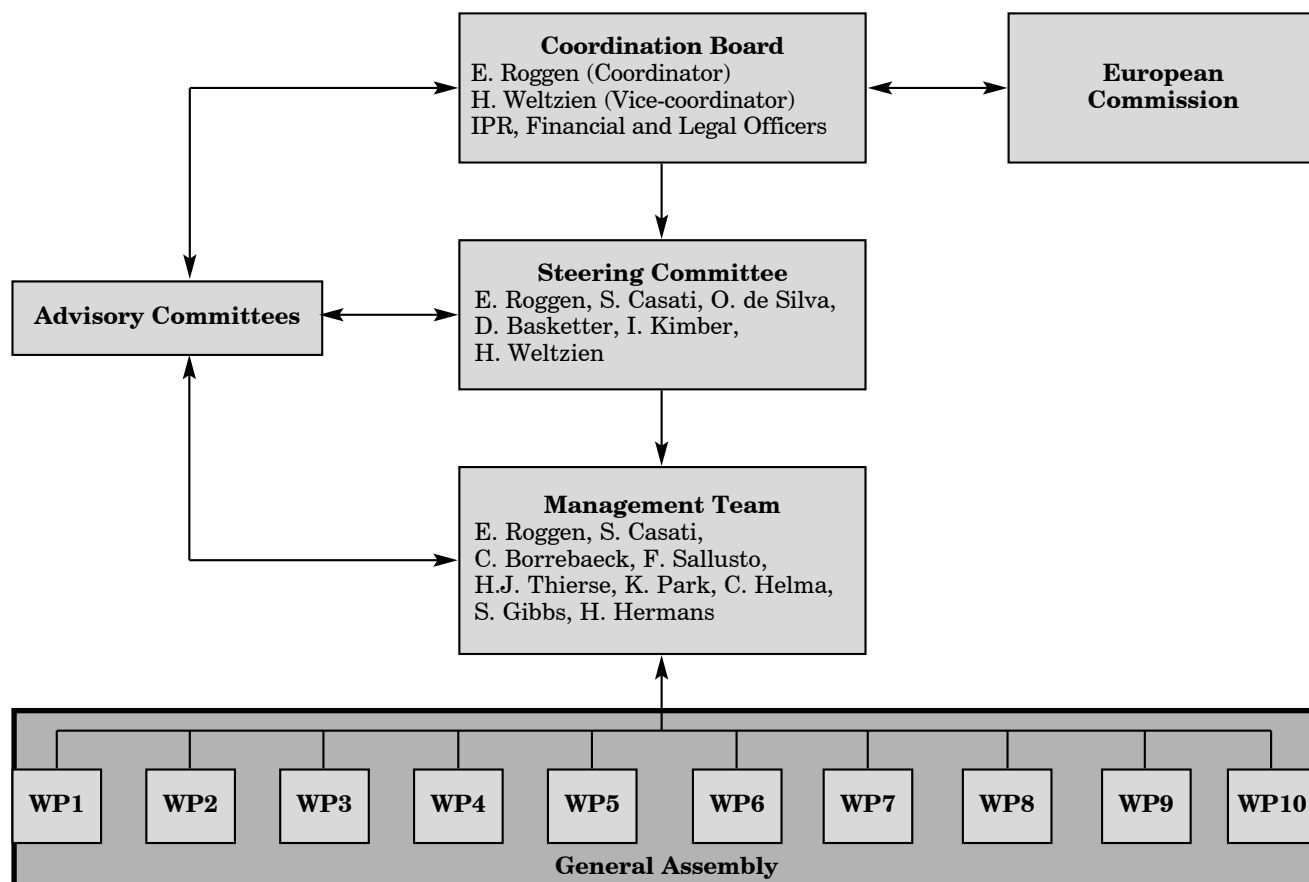
WP8 will involve the application of the stored information for the optimisation and refinement of newly developed or existing tests, up to a level which meets the ECVAM criteria for entering the prevalidation process (5). Originally, this WP was intended to start after 36 months. However, the progress made within the scientific module during the first 12 months (6) has made it possible for the activities of WP8 to be initiated earlier, with the aim of evaluating and improving selected tests.

Technology transfer and the dissemination of results are the tasks of WP9. Dissemination has the ultimate goal of ensuring early awareness and easier adoption of the *in vitro* test methods by various industry sectors as key end users, academia and regulators. IVTIP and COLIPA will ensure technology transfer and dissemination to the industrial sectors covered by their memberships, and to academia and regulators. Both platforms will be supported by ECOPA in addressing industry and academia, as well as governments, animal welfare organisations and consumers. Technology transfer, in the sense of training and education, will also be provided.

Apart from dissemination via regular meetings of stakeholder groups, all the participants are providing the proper dissemination of project results through their own channels, including publications in peer-reviewed scientific journals, oral and poster presentations at (inter)national congresses, and via their own networks. WP9 is also responsible for the construction and maintenance of a dedicated website ([www.sens-it-iv.eu](http://www.sens-it-iv.eu)), both for the purpose of internal communication and for the dissemination of results.

## Project Management (WP10)

The flow of management responsibilities within Sens-it-iv is shown in Figure 2. The overall management of the project is the responsibility of a Coordination Board (CB), composed of the Coordinator, Dr Erwin Roggen (Novozymes, Denmark), and the Vice-coordinator, Dr Hans-Ulrich Weltzien (Max Planck Institute, Germany). They are supported by a team of legal, financial and Intellectual Property Rights (IPR) officers, employed by Novozymes. The CB is also the direct contact body between the Sens-it-iv consortium and the EC, and

**Figure 2: The advisory committees interact with more groups in the project**

deals with the overall management of the project with the support of a Steering Committee (SC).

The SC, chaired by the Coordinator, assumes overall responsibility toward the Management Team (MT), for liaison between participants, for analysing and approving the results generated within the different WPs, for the proper administration of the project, and for the implementation of the provisions contained in the Consortium Agreement. All decisions are taken by simple majority. The SC has the right to set up Advisory Committees to advise and support it in the proper management and coordination of the project. These committees should only have an advisory role.

The MT consists of the 10 WP leaders. It decides on matters relating to approval of the scientific and technical aspects of the implementation plans before their submission to the EC, the acceptance of new parties, as well as the exclusion of old participants, and possible changes to the Consortium Agreement. Meetings of the MT are chaired by the Coordinator of the project, who is also the leader of WP10.

The WP leaders represent their respective WPs in the MT, and coordinate the given tasks. They are responsible for the necessary resources and for

assuring the scientific quality of the work within their WPs. They are in charge of solving technical problems, discussing approaches and methodologies with the other members of the WP, preparing the half-yearly progress reports, as well as the annual progress reports for their WPs, maintaining contact with all the participants, and ensuring the flow of communication both inside and outside the WP.

The General Assembly is composed of all the consortium participants, and for this reason, has an active participation in the decision-making process by approving or not approving decisions taken by the CB and the SC, including financial and technical issues, the initiation of controls and audit procedures in the event of problems with specific partners, and the inclusion or expulsion of consortium partners. Furthermore, the General Assembly addresses issues related to IPRs. The General Assembly meets at least once a year, is chaired by the Coordinator of the project, and approves decisions supported by a two-thirds majority of votes.

In addition to the defined decision-making structure, the issuing of regular reports on current research progress and deliverables, assists the project management with decisions on which technologies are to be incorporated into the second phase of

**Table 1: List of Sens-it-iv project participants and their involvement in WPs and in other management structures**

| Name                                                       | Company                                                                                                                                           | Country                                       | Coordination board | Steering committee | Management team | Work package leader | Work package                                       |
|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------|--------------------|-----------------|---------------------|----------------------------------------------------|
| E. Roggen<br>H.J. Thierse<br>S. Casati<br>I. Kimber        | Novozymes A/S<br>Ruprecht Karls Universität Heidelberg<br>ECVAM, EC Joint Research Centre<br>Syngenta Ltd                                         | Denmark<br>Germany<br>Italy<br>UK             | ×                  | ×                  | ×               | WP10<br>WP5<br>WP1  | 1, 2, 7, 8, 9, 10<br>1, 3, 5, 7, 8<br>1, 9<br>3, 8 |
| S. Teissier<br>D. Basketter<br>C. Borrebaek<br>F. Sallusto | L'Oréal SA<br>Unilever<br>Lunds Universitet<br>Institute for Research in Biomedicine                                                              | France<br>UK<br>Sweden<br>Switzerland         |                    | ×                  | ×               | WP2 WP4<br>WP3      | 2, 7, 8<br>1<br>2, 4, 7, 8<br>3, 8                 |
| S. Gibbs<br>K. Park<br>J. McLeod<br>A. Braun               | VU University Medical Centre<br>University of Liverpool<br>University of West of England<br>Fraunhofer Institute                                  | The Netherlands<br>UK<br>UK<br>Germany        |                    |                    | ×               | WP8<br>WP6          | 2, 3, 8<br>1, 5, 6, 7<br>2, 5, 8<br>2              |
| E. Corsini<br>I. Nelissen<br>M. Assenmacher<br>A. Cavani   | Università degli Studi di Milano<br>Vito<br>Miltenyi Biotec GmbH<br>Istituto Dermopatico dell' Immacolata (IDI)                                   | Italy<br>Belgium<br>Germany<br>Italy          |                    |                    |                 |                     | 2<br>2, 8<br>3<br>3                                |
| H.U. Weltzien<br>E. Maggi<br>M. Marrec-Fairley<br>P. Aeby  | Max Planck Institute for Immunobiology<br>Università di Firenze<br>Colipa<br>Procter & Gamble                                                     | Germany<br>Italy<br>Belgium<br>Switzerland    | ×                  | ×                  | ×               |                     | 10<br>3<br>9<br>2, 8                               |
| J.A. Vericat<br>H. Hermans<br>H. Merck<br>J.P. Lepotttevin | <i>In Vitro</i> Testing Industrial Platform<br>Scientific Writing & Consultancy<br>Universitätsklinikum Aachen (RWTH)<br>Université Louis Pasteur | The Netherlands<br>Spain<br>Germany<br>France |                    |                    | ×               | WP9                 | 10<br>9<br>6<br>1, 6                               |
| A.G. Martin<br>C. Helma<br>S. Martin<br>O. De Silva        | Proteomika SL<br>Universität Freiburg Computer Science<br>Universität Freiburg Faculty for Medicine<br>L'Oréal                                    | Spain<br>Germany<br>Germany<br>France         |                    |                    | ×               | WP7                 | 5<br>1, 7<br>3                                     |

the proposal (go/no-go decisions). Major milestones provide a clear statement of results obtained, problems encountered, and feasibility of achieving the WP objectives. These milestones should assist project management in the early identification of any scientific and technological bottlenecks that may delay the achievement of the final goal.

The participants in the Sens-it-iv consortium, and their respective responsibilities within the Sens-it-iv project, are listed in Table 1. Many participants have various roles in the project, by being members of more WPs and by participating in a number of management bodies. This overlap of responsibility is helpful in assuring communication flow within the project and effectiveness in the fulfilment of deliverables deadlines.

## Conclusions

Good management practice is subject to a set of general rules. These rules, while often perceived as 'common sense', are not always implemented. This often results in distrust and tension within a project group. In Sens-it-iv, these general rules were agreed in advance by the consortium participants, and were designed to specifically tailor the *modus operandi* to the needs of the project. At the start of the project, accepted clear descriptions of the responsibilities of the different project levels were established. Furthermore, a detailed roadmap with scientific and management milestones and deliverables was provided, with a toolbox to accommodate the needs that would arise during the course of the project itself: the Consortium Agreement. The low threshold between the various management levels within the project, and the involvement of all the partners in planning and in problem identification and solving, facilitates active monitoring and early decision-making. Any corrective action or amendment to the original plans must be agreed upon, to ensure common understanding of the new goals, deliverables and milestones. Moreover, management within the Sens-it-iv project is supported by the establishment and maintenance of proper com-

munication tools, in order to ensure the flow of relevant information among all the participants.

Project management is not only about coordinating research activities and training people. It also includes data management and the management of intellectual properties developed within the project. Both these activities are an integral part of this project.

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