



**ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT**

**Advice on an application for deliberate release of a GMO for research and development purposes**

**Applicant:** Acambis Research Ltd

**Application:** To release live attenuated *Salmonella typhi*, created by genetic modification, as part of a human clinical trial to test the effectiveness of a vaccine against typhoid.

**Ref:** 03/R35/2<sup>1</sup>

**Date:** 24<sup>th</sup> March 2003

**Advice of the Advisory Committee on Releases to the Environment to the Secretary of State under section 124 of the Environmental Protection Act 1990**

ACRE is satisfied that all appropriate measures have been taken to avoid adverse effects on human health and the environment from the proposed release and sees no reason for the release not to proceed on the following condition.

The holder of the consent shall notify the following information at the times shown:

The effects of the release as authorised by the consent, for the assessment of any risks there are of damage to human health and the environment from the genetically modified organisms concerned. This should be in the form of reports submitted:

- by one month after the date of administration of the GMO at each of the four stages of the dose escalation protocol; to evaluate shedding of the GM bacteria during the clinical trial by assessment of the quantity and period over which shedding of the GMO from volunteers occurred. This to be provided with a report on the general health of the volunteers.

**Background**

ACRE considered this application at their meeting of the 20 January 2003 and in subsequent correspondence, as with previous clinical trial applications the Committee requested the expert advice of the Director of the Laboratory of Enteric Pathogens at the Central Public Health Laboratory.

<sup>1</sup>Application reference 03/R35/2 dated 2 January 2003 taking into account all information and amendments as in the applicant's letter dated 26 February 2003

### The GM strain

This application from Acambis is to release *Salmonella typhi* which has been genetically modified to contain deletions within the open reading frames of the structural genes encoding *aroC*, *aroD* and *htrA*. These mutations cause the GMO to be less pathogenic and less able to survive in the environment. The GMO does not contain any inserted genetic material. This GMO is being proposed as a candidate vaccine for use against typhoid fever.

### The clinical trial

The purpose of the release is to allow for phase 1 clinical trials of this vaccine in adult human volunteers. The proposed release is to take place at the Chiltern Clinical Research Centre in Slough. Up to 45 adult volunteers will be vaccinated in a dose escalation protocol. After administration of the vaccine the volunteers will be allowed home the same day to go about their normal activities. All trial participants will be provided with health education regarding prevention of transmission of enteric pathogens, including personal and food preparation hygiene. It is expected that the GMO will be shed in the stools of volunteers from which it will enter the sewage system along with other commensal enterobacteria and be inactivated. Volunteers will not be allowed to leave England until it has been demonstrated that they are no longer disseminating the GMO, in addition travel will be limited due to a requirement to attend the trial centre daily for 9 days post vaccination. In the event that a subject is required to leave the country in an emergency or that adverse effects from the vaccine strain are experienced, appropriate antibiotics that are effective against the GMO will be administered to the volunteers..

### **Comment**

Typhoid is an acute life threatening disease characterised by fever, headache, and malaise. It is transmitted in food and drink where sanitation is not kept to a high standard, for example in Africa and Asia. In reviewing this application ACRE noted that there are several vaccines currently available for use against typhoid, none of which are 100% effective. One of the vaccines commonly used consists of an oral live attenuated strain of *Salmonella typhi* in which the attenuating mutations are not clearly defined. ACRE acknowledged that the GMO proposed to be released by Acambis is also a live attenuated strain of *Salmonella typhi*. However in this case the mutations have been created by specific targeted genetic manipulation hence the risk assessment can be based on this molecular knowledge.

In assessing this application ACRE raised a number of questions which were referred back to the applicants. These included clearer definition of the role of the *htrA* gene and clarification on the level of resistance of the GMO to specific antibiotics. In particular ACRE were disappointed that the applicant had made an assumption that treatment of waste water in England always involved the use of chlorinated water. The applicants were asked to revise their application from the perspective that waste will enter unchlorinated water. The committee was content with the responses received and were satisfied that following dissemination of the GMO in stools of vaccinated volunteers, the GMO is unlikely to survive in sewage treatment systems. In addition ACRE considered the possibility that the GMO may not always be disseminated into the sewers but into the wider environment. In this unlikely event, the GMO is expected to survive only for a short period and not to replicate.

ACRE were satisfied that the detection methods specified in the application were sufficient to identify the GM *S typhi* within a diverse population of enteric bacteria. These methods are adequate for the purpose of monitoring the occurrence and extent of shedding during the trial. The Committee requested information on

monitoring of the volunteers and was satisfied with the proposed plan, requesting that a report of this monitoring be provided after each stage of the dose escalation protocol for evaluation of the level of shedding of the GMO.

ACRE concluded that based on the risk assessment provided by the applicant that the risk from this particular GMO to human health and the environment is low. This is based, in part, on the fact that the organism does not survive in the environment and is effectively destroyed in the sewage system along with a significant amount of other enteropathogens which are released in exactly the same manner in the UK on a daily basis, including wild type pathogenic *Salmonella typhi*.

### **Items arising from public representations**

ACRE considered the scientific issues raised in the one representation received from the public with respect to this application from Acambis. The Committee noted the comments raised regarding routes of discharge of the GM bacteria from human volunteers, controls to ensure that the GMOs are inactivated and the effects of the release on non-target species. ACRE was content that all science-based issues raised in the public representation had been considered thoroughly during the Committee's assessment of the dossier and that no outstanding issues remained.