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The Organisation of Jointly-Sponsored (ECO) Toxicological Studies

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THE ORGANISATION OF JOINTLY-SPONSORED (ECO) TOXICOLOGICAL STUDIES

A - INTRODUCTION

ECETOC members sometimes participate in (eco) toxicological studies, jointly sponsored at a contract laboratory. In the absence of a central body with the capacity to administer such studies, experience has shown that various difficulties can arise in initiating the formation of a group and in organising the action thereafter.

In this document are set out some principles and details to guide the organisation of such groups, so that they may anticipate the various problems which can arise, and have a basis for resolving them.

There are, broadly, two types of group to be considered.

1. European Group - where all participants, or a large majority, are European-based companies and the majority are ECETOC members. ECETOC could legitimately manage such a group. The presence of a few non-ECETOC companies would lower the cost to our members. Such companies could be asked to pay a realistic management fee to ECETOC.

2. World-wide Group - It would not normally be ECETOC's role to manage a world-wide group, unless it had been initiated by ECETOC and contained a majority of ECETOC members. There seems no advantage in ECETOC acting as a middle-man for financial/organisational matters between its members and the administrative centre of the group, but if ECETOC members wished to meet as a European sub-group, a) to discuss the preliminary arrangements (basis of payment, protocol etc.) prior to joining the world-wide group, and b) to discuss technical matters during the course of the work, this could be arranged.

   The existence of a European sub-group would double the meetings, and work, for members who attended the world-wide group as well, and it would be wise to consider what the purpose of the sub-group is and whether there would be advantages in creating it.

B - INITIATION OF A GROUP

Stage 1. When ECETOC learns that a proposal for an (eco) toxicological study is being seriously considered or requested, for a compound likely to be of interest to members, it will distribute the information, and request members to indicate whether they wish to meet for a preliminary discussion, without commitment. The interested members will discuss the factors for and against proceeding and will determine how many members wish to go ahead.

Stage 2. If sufficient members wish to proceed further, a meeting will be arranged to consider :

a) defining the scope and objectives of the study ;
b) drafting a test protocol for the purpose of getting cost estimates. This must be done by a group of (eco) toxicologists from member companies ;
c) choosing contract laboratories, and approaching them for cost estimates and possible starting dates ;
d) Agreeing the basis for cost sharing - see Appendix 1.

Stage 3. When information from stage 2 is available, and in particular when the cost is known, members have to take a final decision whether to proceed. If enough companies still wish to go ahead then : a choice of contract laboratory has to be made ; one company has to agree to supply the test substance (see below) ; and a "Formal Group Agreement" has to be drawn up.

Which company supplies the test substance will to some extent depend on the location of the chosen contract laboratory. A specification, including any necessary impurity levels, should be drawn up and the supplying company should produce a cost estimate for isolating, analysing, packaging and transporting the material, and for any technical advice which may have to be given to the testing laboratory.

C - FORMAL GROUP AGREEMENT

This is a legally-binding document setting out the membership, aims, obligations and mode of operation of the Group. The following items need to be considered, but may not all need to be put into the Agreement.

1. Membership - The legally correct name and European address of each member should be specified. Companies wishing to join the Group at any later stage will pay the full fee (adjusted to allow for the larger membership, but always on the agreed cost-sharing basis), and will have full rights to participation, and to past documents and information.
Membership of the Group will cease if :

a) a company gives 6 months notice of resignation. Membership ends at the expiry of 6 calendar months from the date of notice, and the company loses rights to any information generated after this date. The resigning member has no rights to repayment of any sum paid before the expiry date, but is liable to pay any sums due before that date;

b) any sum payable by the company is more than 6 months in arrears.

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2. Aims - The scope and objectives of the study should be clearly defined. Different companies may have different reasons for participating (eg industrial hygiene aspects or consumer product aspects), and these requirements will influence the type of study required and the eventual use of the results. All members should thoroughly understand and agree the protocol.

3. Financial obligations.

a) The basis of cost sharing, and an estimate of the total cost (plus Value Added Tax and a contingency) should be stated. The payments to be made by each member should be listed in cash amount.

b) The obligation of members to meet payments to the contract laboratory at fixed intervals should be stated.

c) Payments by members to the company supplying the test substance should be specified, on the same cost-sharing basis as for the payments for the study as a whole.

d) Expenditure in excess of the total stated in a) above should require a formal agreement within the terms of the existing agreement, or a new document of agreement.

e) Each company should agree to pay the expenses of its staff attending Management Group meetings, assuming that all or most participants are represented. For any Sub-groups, which may be much smaller, the Management Group should decide whether Sub-group member companies pay their own expenses, or whether they should be paid by the Group as a whole. Note that this would involve much detailed accounting, and may be counter-productive in terms of time and money. Where an individual, or a small group, has to make exceptional visits, the Management Group should decide whether the costs should be carried by the Group.

f) For companies in the Group who are not ECETOC members, a reasonable management fee should be paid to ECETOC if it is providing an administrative service.

g) When the Group terminates its work it will either repay to members any remaining money on the original cost-sharing basis, or if the amount is small it could consider donating it to ECETOC to cover part of its servicing costs to the Group.

4. Mode of operation - It has, in past joint studies, proved very important to separate the general/financial/administrative management from the technical/scientific management. Thus a Management Group should be formed, preferably with all participants represented, for the overall execution of the work. This Group should appoint an (Eco)Toxicological Sub-group concerned solely with scientific/technical matters, and reporting to the Management Group.

It is important for the efficient functioning of the study that one person on the Management Group should be nominated for day-to-day administrative contacts with the contract laboratory (ECETOC could provide this service), and that one person from the (Eco)Toxicology Sub-group be nominated for day-to-day technical matters (this would have to be an expert, not ECETOC). The latter person should be

empowered by the Management Group to take emergency decisions on technical matters where a decision affecting the validity of the study is urgently needed.

Thus this section of the agreement should cover the following.

a) setting up of a Management Group ; broad definition of its responsibilities ; quorum ; voting procedures (it is strongly suggested that unanimity is not required) ; choice of a member to be the responsible contact with the test laboratory for administrative matters.

b) setting up of an (Eco)Toxicology Sub-group ; broad definition of its responsibilities, quorum, voting procedure ; choice of a member to be responsible for day-to-day technical contacts with the test laboratory and to be empowered to take urgent technical decisions (to be reported to the Sub-group and Management Group immediately).

c) A specification of which country's law governs the agreement.

d) A statement of intent to act jointly if there develops a need to inform governments, employees, trade unions etc. of matters arising from the study - see section G.

e) a statement specifying

i) the form of any announcement about the initiation of the study ;

ii) the form of publication, if any, of the final results of the study.

D - CONTRACT WITH TEST LABORATORY

One of the first tasks of the Group is to draw up the contract in cooperation with the test laboratory. The document, to be prepared in draft for approval by the Group, should include :

1. The legally-correct names and addresses of the companies participating ;
2. An adequately detailed test protocol
3. A statement defining the test substance, and its specification, including any necessary impurity levels ;
4. An estimate of the date on which experimental work will start ; its duration ; duration of the subsequent operations (histopathology etc.) ; date of issuing the final report. These estimates are not binding on the contract laboratory but are needed to determine the timing of periodical payments ;
5. An estimate of the total cost ;
6. A formula for adjusting costs to inflation, for all but short studies (see appendix 2) ;
7. A description of the periodical payments to the laboratory ;

8. A specification of the approximate frequency of progress-monitoring visits to the laboratory, and of matters to be dealt with during such visits, especially the right to examine all slides ;

9. A description of the frequency and content of interim reports to be provided by the laboratory, normally for consideration at progress-monitoring visits. To keep down the administrative costs, these should be the minimum necessary to ensure that the study is adequate in all respects ;

10. A description of the format and contents of the final report from the laboratory. This may be influenced by the requirements of legislatory authorities, as even for existing compounds the testing and reporting standards expected may well be equal to those legislated for new compounds ;

11. A requirement that at a defined stage in the experimental part of the study a firm date will be fixed for the issuing of the final report by the test laboratory ;

12. An assurance that the work will meet the requirements of a currently-recognised standard of Good Laboratory Practice.

13. A specification of which country's law covers the contract.

14. A requirement that the contract laboratory keeps specified information confidential.

When members of the Group and the test laboratory have agreed the text of a contract, original documents (not copies) will be signed by each Group member and by the test laboratory. Every document should carry every signature, and all parties should have an original. Each participant is responsible for obtaining his own legal assessment before signing.

F - PAYMENTS

a) To test laboratory. It is normal practice in long studies for the sponsoring group to make part payments as the work progresses. A compromise must be sought between the need of the test laboratory to have sufficient funds to start and continue the work, and the need to protect the sponsors from gross failure to meet the contract.

For studies lasting 2 years or more the following scheme is commonly adopted :

Payment, % of estimated total	Date of payment
30	Signature of contract with laboratory
20)	At end of 1st, 2nd and 3rd quarter of the total period of experimental work.
20)	
20)	
10	Receipt of final report in the form specified in the contract.

For studies lasting about 90 days, 60% should be paid on signing the contract and 40% on receipt of the final report in the form specified in the contract.

For acute studies, normally lasting much less than 90 days the whole payment is usually made on receipt of the final report.

b) Payments by members. As soon as the "Formal Group Agreement" (see section C above) is signed, members should contact the Financial Dept. of their company to warn them of the periodical payments to be made. There can be significant delays if a good mechanism is not established with the Accounts Department beforehand.

Where ECETOC is managing the Group a separate current account will be established, into which payments from members are made, and from which the laboratory is paid. ECETOC would be responsible for these operations, and for rendering an account to members. On no account will ECETOC money be used in the affairs of the Group except for that which is spent directly in providing a service to the Group.

By careful timing of requests for payment by members, and actual payments to the laboratory, the prolonged accumulation of large sums of money could be prevented. This will avoid the problem of having to re-distribute any substantial interest to members. As seen from Appendix 3, the likely interest is negligible if the money is held for a short time in a current account. It is suggested that at the end of the Group's activities the accumulated interest be paid to ECETOC to meet a (very small) proportion of the servicing expenses. Should it happen that larger sums of money accumulate from interest on cash which has to be held on deposit (higher rate of interest), it should at the decision of the Management Group be paid back to members on the cost-sharing basis.

G - PROCEDURE FOR COMMUNICATING INTERIM OR FINAL RESULTS.

One of the problems for joint groups arises when the studies reveal adverse results which have to be communicated to governments, employees, customers and unions. Obligations vary from country to country, and the form and timing of any such announcements needs to be anticipated.

It would be incorrect to put a detailed plan of action into the "Formal Group Agreement" since this cannot over-ride each members' legal obligations in his own country. However, the following could be noted in the agreement :

1. The form and the timing of each member's obligatory actions
2. The intent of the Management Group to meet urgently, for discussion, as soon as an adverse effect is reported;
3. The need to assess the initial evidence of adverse effects,

to ensure that they are firm enough to justify communication to others ;

4. The intent to draft a common statement, appropriate to the findings and to the intended recipients ;
5. The obligation of each member to report the effect to his government, employees etc., and to do this unilaterally if the Group has not produced an agreed text before the last possible date ;
6. The obligation of each member to inform all members immediately of action taken to inform others. The text of such communications must be provided unless it is an already agreed text.

The rights of the contract laboratory to the copyright, and to publish the report, should be specified. The rights of the participating companies to reproduce and use the contents of the Final, and any interim Reports should be specified.

NOTE- We have in the ECETOC office an actual detailed agreement with a contract laboratory, which could be made available as a model to companies needing it. It has been made anonymous by removal of all references to actual organisations or products, etc.

L. Turner

L. TURNER

APPENDIX 1

POSSIBLE BASES OF COST SHARING

1. Equal shares - Administratively the most simple, but is the least likely to be agreed when there are large differences between the tonnages produced and/or used by Group members.

2. Nameplate capacity - Factors to be considered are :

   - nameplate capacity for production of substance ;
   - nameplate capacity for conversion of substance, which could be by the primary producer or by a company which buys-in the substance ;
   - relevant date to which the information on capacity applies.

   Shares of payment could be pro-rata on the nameplate capacity, or could be weighted differently between producers and users.

3. Actual tonnage produced/used - This poses the following problems :

   - over what period ?
   - it varies from period to period ;
   - confidentiality of information ;

   shares of payment would be pro-rata.

4. Turnover - This is probably the most difficult basis :

   - confidentiality of commercial information ;
   - over what period ?
   - what turnover figure would be taken for a co-polymer or formulation containing only a small percentage of the substance ?

   Note that if ECETOC acted as manager, problems of confidentiality could be resolved by ECETOC receiving in confidence the individual figures and making the pro-rata calculations.

APPENDIX 2

ALLOWANCE FOR INFLATION

The following periods of time are important.

a) period from signing contract to start of experimental work. This could be several months for heavily-loaded test laboratories.

b) duration of experimental work up to completion of histopathology.

c) analysis of results and writing of final report.

Where a) + b) + c) is less than 12 months, the test laboratory can be asked to present an estimate of total cost which already includes its own allowance for inflation. No further discussion of inflation will be necessary.

Where a) + b) + c) is more than 12 months (it could well be 3 years for life-time animal studies) the effect of inflation on costs should be reviewed at the end of the 12th and 24th month, from the start of experimental work, with the following factors in mind :

i) in a life-time carcinogenicity study, expenditure during the exposure phase is fairly even, and a simple time-based, inflation formula will suffice. For the post-exposure work the rate of expenditure can change markedly ;

ii) for a mixture of shorter term (acute, 90-day etc.) studies, expenditure per month or per quarter may vary considerably and more complicated agreement may be necessary.

iii) an official cost-of-living index, for example of the country in which the test laboratory is situated, should be agreed as the basis for inflation calculations.

iv) depending on the type of work involved, an appropriate formula for adjusting costs to inflation should appear in the contract.

APPENDIX 3

ACCUMULATION OF INTEREST

Take a "worst-case" example : a carcinogenicity study costing £ 200,000, where on average each part-payment remained in the current account at 0,5% interest per year for 2 months, ie. before being sent to the test laboratory.

Accumulated interest in 2 months = 0.5/6 %

On £ 200.000, this = £ 170.

The administrative costs of re-distributing this among members, and the sending of receipts etc. would use up much of this sum.