

**International Agency for Research on Cancer**



**World Health  
Organization**

**STATUTE,  
RULES AND  
REGULATIONS**

**Fourteenth Edition**

Including amendments up to May 2014

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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STATUTE

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**ESTABLISHMENT OF AN  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER**

**Resolution WHA18.44 of the Eighteenth World Health Assembly**

The Eighteenth World Health Assembly,

Cognizant of Article 18 of the Constitution which provides, *inter alia*, that one of the functions of the Health Assembly shall be to establish such other institutions as it may consider desirable, with a view to promoting and carrying on research;

Considering that the Governments of the Federal Republic of Germany, France, Italy, the United Kingdom of Great Britain and Northern Ireland, and the United States of America have agreed to sponsor the creation and to participate in the functioning of an International Agency for Research on Cancer in accordance with the provisions of its Statute;

Considering that many governments have expressed their interest in the creation of such an Agency; and

Considering resolution WHA17.49 of the Seventeenth World Health Assembly,

DECIDES to establish an International Agency for Research on Cancer which shall carry on its functions in accordance with the provisions of its Statute (annexed).

*Twelfth plenary meeting, 20 May 1965*

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INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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**STATUTE OF  
THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER<sup>1</sup>**

*Article I – Objective*

The objective of the International Agency for Research on Cancer shall be to promote international collaboration in cancer research. The Agency shall serve as a means through which Participating States and the World Health Organization, in liaison with the International Union against Cancer<sup>2</sup> and other interested international organizations, may cooperate in the stimulation and support of all phases of research related to the problem of cancer.

*Article II – Functions*

In order to achieve its objectives, the Agency shall have the following functions:

1. The Agency shall make provision for planning, promoting and developing research in all phases of the causation, treatment and prevention of cancer.
2. The Agency shall carry out a programme of permanent activities. These activities shall include:
  - (a) the collection and dissemination of information on epidemiology of cancer, on cancer research and on the causation and prevention of cancer throughout the world;
  - (b) the consideration of proposals and preparation of plans for projects in, or in support of, cancer research; such projects should be designed to make the best possible use of any scientific and financial resources and special opportunities for studies of the natural history of cancer which may arise;
  - (c) the education and training of personnel for cancer research.
3. The Agency may arrange for the carrying out of special projects; however, such special projects shall be initiated only upon the specific approval of the Governing Council, based upon the recommendation of the Scientific Council.
4. Such special projects may include:
  - (a) activities complementary to the permanent programme;
  - (b) the demonstration of pilot cancer prevention activities;
  - (c) the encouragement of, and the giving of assistance to, research at the national level, if necessary by the direct establishment of research organizations.
5. In carrying out its programme of permanent services or any special projects the Agency may collaborate with any other entity.

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<sup>1</sup> Pursuant to its Articles III and XI, the Statute entered into force on 15 September 1965, by which date five of the States that took the initiative in proposing the International Agency for Research on Cancer had given the undertaking referred to in Article III. Amendments adopted by the Seventh, Ninth, Twenty-Seventh, Thirty-First, Fiftieth and Fifty-Third Governing Councils (resolutions GC/7/R5, GC/9/R13, GC/27/R14, GC/31/R7, GC/50/R15 and GC/53/R9) came into force on 19 May 1970, 23 May 1972, 15 May 1986, 17 May 1990, 24 May 2008 and 24 May 2011 respectively, and are incorporated in the present text.

<sup>2</sup> As from August 2010, full English name became "Union for International Cancer Control" (UICC).

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*Article III – Participating States*

Any Member of the World Health Organization may, subject to the provisions of Article XII, participate actively in the Agency by undertaking, in a notification to the Director-General of the World Health Organization, to observe and apply the provisions of this Statute. In this Statute, Members which have made such a notification are termed "Participating States".

*Article IV – Structure*

The Agency shall comprise:

- (a) the Governing Council;
- (b) the Scientific Council;
- (c) the Secretariat.

*Article V – The Governing Council*

1. The Governing Council shall be composed of one representative of each Participating State and the Director-General of the World Health Organization, who may be accompanied by alternates or advisers.
2. Each member of the Governing Council shall have one vote.
3. The Governing Council shall:
  - (a) adopt the budget;
  - (b) adopt financial regulations;
  - (c) control expenditure;
  - (d) decide on the size of the Secretariat;
  - (e) elect its officers;
  - (f) adopt its own rules of procedure.
4. The Governing Council, after considering the recommendations of the Scientific Council, shall:
  - (a) adopt the programme of permanent activities;
  - (b) approve any special project;
  - (c) decide upon any supplementary programme.
5. Decisions of the Governing Council under subparagraphs (a) and (b) of paragraph 3 of this Article shall be made by a two-thirds majority of its members who are representatives of Participating States.
6. Decisions of the Governing Council shall be taken by a simple majority of members present and voting, except as otherwise provided in this Statute. A majority of members shall constitute a quorum.
7. The Governing Council shall meet in ordinary session at least once in each year. It may also meet in extraordinary session at the request of one-third of its members.
8. The Governing Council may appoint subcommittees and working groups.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Article VI – The Scientific Council*

1. The Scientific Council shall be composed of highly qualified scientists, selected on the basis of their technical competence in cancer research and allied fields. Members of the Scientific Council are appointed as experts and not as representatives of Participating States.
2. Each Participating State may nominate up to two experts for membership in the Scientific Council and, if a Participating State makes such a nomination, the Governing Council shall appoint one of them.
3. In identifying experts to be considered for appointment to the Scientific Council, Participating States shall take into account advice to be provided by the Chairperson of the Scientific Council and the Director of the Agency concerning the expertise required on the Scientific Council at the time of those appointments.
4. Members of the Scientific Council shall serve for a term of four years. Should a member not complete a term, a new appointment shall be made for the remainder of the term to which the member would have been entitled, in accordance with paragraph 5.
5. When a vacancy arises on the Scientific Council, the Participating State that nominated the departing member may nominate up to two experts to replace that member in accordance with paragraphs 2 and 3. Any member leaving the Scientific Council, other than a member appointed for a reduced term, may be reappointed only after at least one year has elapsed.
6. The Scientific Council shall be responsible for:
  - (a) adopting its own rules of procedure;
  - (b) the periodical evaluation of the activities of the Agency;
  - (c) recommending programmes of permanent activities and preparing special projects for submission to the Governing Council;
  - (d) the periodical evaluation of special projects sponsored by the Agency;
  - (e) reporting to the Governing Council, for consideration at the time that body considers the programme and budget, upon the matters dealt with in subparagraphs (b), (c) and (d) above.

*Article VII – Secretariat*

1. Subject to the general authority of the Director-General of the World Health Organization, the Secretariat shall be the administrative and technical organ of the Agency. It shall in addition carry out the decisions of the Governing Council and the Scientific Council.
2. The Secretariat shall consist of the Director of the Agency and such technical and administrative staff as may be required.
3. The Director of the Agency shall be selected by the Governing Council. The appointment shall be effected by the Director-General of the World Health Organization on such terms as the Governing Council may determine.
4. The staff of the Agency shall be appointed in a manner to be determined by agreement between the Director-General of the World Health Organization and the Director of the Agency.

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5. The Director of the Agency shall be the chief executive officer of the Agency. He shall be responsible for:
  - (a) preparing the future programme and the budget estimates;
  - (b) supervising the execution of the programme and the scientific activities;
  - (c) directing administrative and financial matters.
6. The Director of the Agency shall submit a report on the progress of the Agency and the budget estimates for the next financial year to each Participating State and to the Director-General of the World Health Organization, which shall be distributed to reach them at least thirty days before the regular annual meeting of the Governing Council.

*Article VIII – Finance*

1. The administrative services and permanent activities of the Agency shall be financed by annual contributions by each Participating State.
2. These annual contributions shall be due on 1 January of each year and must be paid not later than 31 December of that year.
3. The level or levels of annual contributions shall be determined by the Governing Council.
4. Any decision to change the level or levels of annual contributions shall require a two-thirds majority of the members of the Governing Council who are representatives of Participating States.
5. A Participating State which is in arrears in the payment of its annual contribution shall have no vote in the Governing Council if the amount of its arrears equals or exceeds the amount of contributions due from it for the preceding financial year.
6. The Governing Council may establish a working capital fund and decide its amount.
7. The Governing Council shall be empowered to accept grants or special contributions from any individual, body or government.

The special projects of the Agency shall be financed from such grants or special contributions.

8. The funds and assets of the Agency shall be accounted for separately from the funds and assets of the World Health Organization and administered in accordance with the financial regulations adopted by the Governing Council.

*Article IX – Headquarters*

The site of the Headquarters of the Agency shall be determined by the Governing Council.

*Article X – Amendments*

Except as provided in Article VIII, paragraph 4, amendments to this Statute shall come into force when adopted by the Governing Council by a two-thirds majority of its members who are representatives of Participating States and accepted by the World Health Assembly.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Article XI – Entry into force*

The provisions of this Statute shall enter into force when five of the States which took the initiative in proposing the International Agency for Research on Cancer have given the undertaking referred to in Article III to observe and apply the provisions of the present Statute.

*Article XII – New Participating States*

After the entry into force of this Statute, any State Member of the World Health Organization may be admitted as a Participating State, provided that:

- (a) the Governing Council, by a two-thirds majority of its members who are representatives of Participating States, considers that the State is able to contribute effectively to the scientific and technical work of the Agency;
- (b) and thereafter, the State gives the undertaking referred to in Article III.

*Article XIII – Withdrawal from participation*

A Participating State may withdraw from participation in the operation of the Agency by notifying the Director-General of the World Health Organization of its intention to withdraw. Such a notification shall take effect six months after its receipt by the Director-General of the World Health Organization.

RULES OF PROCEDURE OF THE GOVERNING COUNCIL

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**RULES OF PROCEDURE OF THE GOVERNING COUNCIL  
OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER<sup>3</sup>**

MEMBERSHIP AND ATTENDANCE

*Rule 1*

The Governing Council shall, in accordance with Article V, paragraph 1, of the Statute of the International Agency for Research on Cancer (hereinafter referred to as the "Agency"), be composed of and be attended by a representative of each Participating State and the Director-General of the World Health Organization or a person designated by him for this purpose. They may be accompanied by alternates and advisers.

*Rule 2*

Subject to the terms of any relevant agreement, representatives of intergovernmental organizations with which the Organization has established effective relations under Article 70 of the Constitution may be invited to participate without vote in the deliberations of meetings of the Governing Council, with respect to items in which they have an interest. Representatives of non-governmental organizations in official relations with the Organization may be invited to participate in the deliberations of the Governing Council in accordance with the Principles Governing Relations between WHO and Non-governmental Organizations<sup>4</sup>.

CREDENTIALS

*Rule 3*

Each Participating State shall communicate to the Director of the Agency the name of its representative as well as of any alternate and adviser before each session of the Governing Council.

SESSIONS

*Rule 4*

The Governing Council shall hold at least one regular session a year. It shall determine at each session the time and place of its next session.

Notices convening the Governing Council shall be sent by the Director of the Agency, at least six weeks before the commencement of a regular session, to Participating States, to the Director-General and to the organizations referred to in Rule 2 invited to be represented at the session.

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<sup>3</sup> Text adopted by the Governing Council at its first session (23–24 September 1965) and amended at its Thirteenth, Twenty-Third and Thirty-Eighth sessions (resolutions GC/13/R3, GC/23/R12 and GC/38/R6).

<sup>4</sup> Reproduced in **Basic Documents** of the World Health Organization.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Rule 5*

The Director of the Agency shall also convene the Governing Council at the request of one-third of its members. The request shall be addressed to him in writing and shall state the reason for the request. In this case, the Governing Council shall be convened within thirty days following receipt of the request.

The agenda of such a session shall be limited to the questions having necessitated that session.

*Rule 6*

The meetings of the Governing Council shall be held in private unless the Governing Council decides otherwise.

AGENDA

*Rule 7*

The provisional agenda of each session shall be drawn up by the Director of the Agency in consultation with the Chairman. It shall be dispatched with the notice of convocation to be sent in accordance with Rule 4 or Rule 5, as the case may be.

*Rule 8*

Except in the case of sessions convened under Rule 5, the provisional agenda of each session shall include, *inter alia*:

- (a) all items the inclusion of which has been prescribed by the World Health Assembly or by the Executive Board;
- (b) all items the inclusion of which has been prescribed by the Governing Council at a previous session;
- (c) any item proposed by a Participating State or by the Director-General;
- (d) any item proposed by the Scientific Council;
- (e) any item proposed by the Director of the Agency.

*Rule 9*

Except in the case of sessions convened under Rule 5, the Director of the Agency may, in consultation with the Chairman, include any question suitable for the agenda which may arise between the dispatch of the provisional agenda and the opening day of the session in a supplementary agenda which the Governing Council shall examine together with the provisional agenda.

OFFICERS

*Rule 10*

The Governing Council shall elect as its officers a Chairman, a Vice-Chairman and a Rapporteur from among the representatives of the Participating States each year at a regular session convened under Rule 4. The officers shall hold office until their successors are elected.

RULES OF PROCEDURE OF THE GOVERNING COUNCIL

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*Rule 11*

In addition to exercising the powers which are conferred upon him elsewhere by these Rules, the Chairman shall declare the opening and closing of each meeting of the Governing Council, shall direct the discussions, ensure observance of these Rules, accord the right to speak, put questions and announce decisions. He shall rule on points of order and, subject to these Rules, shall control the proceedings at any meeting and shall maintain order thereat. The Chairman may, in the course of the discussion of any item, propose to the Governing Council the limitation of the time to be allowed to each speaker or the closure of the list of speakers.

*Rule 12*

If the Chairman is unable to preside at a meeting or any part thereof, the Vice-Chairman shall preside. The same procedure shall be followed when the Chairman is unable to attend a session of the Governing Council.

*Rule 13*

If the Chairman is unable to act between sessions, the Vice-Chairman shall act in his place.

COMMITTEES AND WORKING GROUPS

*Rule 14*

The Governing Council may establish within its organization committees or working groups for the study of, and report on, any item on its agenda.

SECRETARIAT

*Rule 15*

The Director of the Agency shall be *ex-officio* the Secretary of the Governing Council and of any of its committees or working groups. He may delegate these functions.

*Rule 16*

The Director of the Agency shall report to the Governing Council on the technical, administrative and financial implications, if any, of all agenda items submitted to the Governing Council.

*Rule 17*

The Director of the Agency, or a member of the Secretariat designated by him, may at any time, make either oral or written statements concerning any question under consideration.

*Rule 18*

The Secretariat shall prepare minutes of the meetings in the working languages and shall distribute them to the representatives as soon as possible after the close of the meeting to which they relate.

Representatives shall inform the Secretariat in writing of any corrections they wish to have made within such period of time as shall be indicated by the Director of the Agency.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Rule 19*

All resolutions, recommendations and other important decisions of the Governing Council, as well as the minutes of the Governing Council, shall be communicated by the Director of the Agency to all Participating States and to the Director-General.

LANGUAGES

*Rule 20*

English and French shall be the working languages of the Governing Council.

*Rule 21*

Speeches made in either of the working languages shall be interpreted into the other working language and Russian. Speeches made in Russian shall be interpreted into both working languages.

*Rule 22*

Any representative may speak in a language other than the working languages and Russian. In this case he shall himself provide for interpretation into one of the working languages. Interpretation into the other languages by interpreters of the Secretariat may be based on the interpretation provided by the representative.

CONDUCT OF BUSINESS

*Rule 23*

A majority of the members of the Governing Council shall constitute a quorum.

*Rule 24*

No representative may address the Governing Council without having previously obtained the permission of the Chairman. The Chairman shall call upon speakers in the order in which they signify their desire to speak. The Chairman may call a speaker to order if his remarks are not relevant to the subject under discussion.

*Rule 25*

A representative may at any time request his alternate to speak and vote on his behalf on any question. Upon the request of the representative or his alternate, the Chairman may allow an adviser to speak but the latter shall not have the right to vote.

*Rule 26*

During the discussion of any matter, a representative may rise to a point of order, and the point of order shall be immediately decided by the Chairman. A representative may appeal against the ruling of the Chairman in which case the appeal shall immediately be put to the vote. A representative rising to a point of order may not speak on the substance of the matter under discussion but on the point of order only.

RULES OF PROCEDURE OF THE GOVERNING COUNCIL

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*Rule 27*

During the course of a debate, the Chairman may announce the list of speakers and, with the consent of the Governing Council, declare the list closed. He may, however, accord the right of reply to any member if in his opinion a speech delivered after he has declared the list closed makes it desirable.

*Rule 28*

The following motions shall have precedence in the following order over all other proposals or motions before the meeting, except a point of order:

- (a) to suspend the meeting;
- (b) to adjourn the meeting;
- (c) to adjourn the debate on the item under discussion; and
- (d) for the closure of the debate on the item under discussion.

*Rule 29*

Subject to Rule 28, any motion calling for a decision on the competence of the Governing Council to adopt a proposal submitted to it shall be put to the vote before a vote is taken on the proposal in question.

*Rule 30*

During the discussion on any matter, a representative may move the suspension or the adjournment of the meeting. Such motions shall not be debated but shall immediately be put to a vote.

For the purpose of these Rules "suspension of the meeting" means the temporary cessation of the business of the meeting and "adjournment of the meeting" the termination of all business until another meeting is called.

*Rule 31*

During the discussion of any matter, a representative may move the adjournment of the debate on the item under discussion. In addition to the proposer of the motion, one speaker may speak in favour of and one against the motion, after which the motion to adjourn the debate shall be immediately put to the vote.

*Rule 32*

A representative may at any time move the closure of the debate on the item under discussion, whether or not any other representative has signified his wish to speak. If request is made for permission to speak against closure, it may be accorded to not more than two speakers, after which the motion shall be immediately put to the vote. If the Governing Council decides in favour of closure, the Chairman shall declare the debate closed. The Governing Council shall thereafter vote only on the one or more proposals moved before the closure.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Rule 33*

A representative may move that parts of a proposal or of an amendment shall be voted on separately. If objection is made to the request for division, the motion for division shall be voted upon. Permission to speak on the motion for division shall be given only to two speakers in favour and two speakers against. If the motion for division is carried, those parts of the proposal or of the amendment which are separately approved shall subsequently be put to the vote as a whole. If all operative parts of the proposal or the amendment have been rejected, the proposal or the amendment shall be considered to have been rejected as a whole.

*Rule 34*

When an amendment to a proposal is moved, the amendment shall be voted on first. When two or more amendments are moved to a proposal, the Governing Council shall first vote on the amendment deemed by the Chairman to be furthest removed in substance from the original proposal and then on the amendment next removed therefrom, and so on, until all the amendments have been put to the vote. Where, however, the adoption of one amendment necessarily implies the rejection of another amendment, the latter amendment shall not be put to the vote. If one or more amendments are adopted, the amended proposal shall then be voted upon.

A motion is considered an amendment to a proposal, if it merely adds to, deletes from, or revises part of that proposal. A motion which constitutes a substitution for a proposal shall be considered as a proposal.

*Rule 35*

If two or more proposals are moved, the Governing Council shall first vote on the proposal deemed by the Chairman to be furthest removed in substance from the proposal first presented and then on the proposal next removed therefrom, and so on, until all the proposals have been put to the vote, unless the result of a vote on a proposal makes unnecessary any other voting on the proposal or proposals still outstanding.

*Rule 36*

A motion may be withdrawn by its proposer at any time before voting on it has commenced, provided that the motion has not been amended, or, if amended, that the proposer of the amendment agrees to the withdrawal. A motion thus withdrawn may be reintroduced by any representative.

*Rule 37*

When a proposal has been adopted or rejected, it may not be reconsidered at the same session unless the Governing Council, by a two-thirds majority of the representatives present and voting, so decides. Permission to speak on a motion to reconsider shall be accorded only to two speakers opposing the motion, after which it shall be immediately put to the vote.

RULES OF PROCEDURE OF THE GOVERNING COUNCIL

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VOTING

*Rule 38*

Subject to the provisions of the Statute of the Agency, each member of the Governing Council shall have one vote. For the purpose of these Rules, the phrase "representatives present and voting" means representatives casting a valid affirmative or negative vote. Representatives abstaining from voting are considered as not voting.

*Rule 39*

Except as otherwise provided in the Statute of the Agency or in these Rules, decisions of the Governing Council shall be taken by a simple majority of the representatives present and voting.

*Rule 40*

The Governing Council shall normally vote by show of hands, except that any representative may request a roll call, which shall then be taken in the English or French alphabetical order of the names of the Participating States in alternate years. The name of the Participating State to vote first shall be determined by lot. The vote of each representative participating in any roll call shall be inserted in the record of the meeting.

*Rule 41*

After the Chairman has announced the beginning of voting, no representative shall interrupt the voting except on a point of order in connexion with the actual conduct of voting.

*Rule 42*

Elections shall normally be held by secret ballot. However, except as concerns the selection of the Director of the Agency, if the number of candidates for elective office does not exceed the number of offices to be filled, no ballot shall be required and such candidates shall be declared elected. Where ballots are required, two tellers appointed by the Chairman from among the representatives shall assist in the counting of votes. The selection of the Director of the Agency shall be decided by secret ballot in accordance with Rule 46.

*Rule 43*

In addition to the cases provided for elsewhere by these Rules, the Governing Council may decide to vote on any matter by secret ballot provided that no secret ballot may be taken on budgetary questions.

A decision under this Rule by the Governing Council whether or not to vote by secret ballot may only be taken by a show of hands; if the Governing Council has decided to vote on a particular question by secret ballot, no other mode of voting may be requested or decided upon.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Rule 44*

Subject to the provisions of Rule 46, when only one elective place is to be filled and no candidate obtains in the first ballot the majority required, a second ballot shall be taken which shall be restricted to the two candidates obtaining the largest number of votes; if, in the second ballot, the votes are equally divided, the Chairman shall decide between the candidates by drawing lots.

*Rule 45*

When two or more elective places are to be filled at one time under the same conditions, those candidates obtaining, in the first ballot, the majority required shall be elected. If the number of candidates obtaining such majority is less than the number of persons or representatives to be elected, there shall be additional ballots to fill the remaining places, the ballots being restricted to the candidates obtaining the greatest number of votes in the previous ballot to a number not more than twice the places remaining to be filled.

*Rule 46*

1. Not less than six months before the opening of a session of the Governing Council during which the Director of the Agency has to be selected, the Director-General of the World Health Organization shall inform each Member State of the Organization of the vacancy of the post.
2. Any Member State of the Organization may propose one or more candidates, attaching to each proposal a curriculum vitae. Proposals with curriculum vitae may also be submitted directly by individuals. Proposals shall be addressed to the Director-General of the World Health Organization so as to reach him not less than twelve weeks before the opening of the Session. If he has so requested, the Director of the Agency holding office may be a candidate without having to be proposed.
3. Not less than ten weeks before the opening of the Session, the Director-General of the World Health Organization shall send to each Participating State copies of all proposals, and their attachments, received within the period specified, and shall indicate whether or not the person holding office is a candidate.
4. If only one or no proposal has been received by the Director-General of the World Health Organization in time for transmission to Participating States in accordance with this Rule, he will inform the Participating States within the period specified in the preceding paragraph. In these cases, during its Session, the Governing Council shall itself establish a list of candidates composed of the names proposed by the representatives present, to which the curricula vitae should be attached. The same procedure will also be followed by the Governing Council in cases where the post of Director of the Agency falls vacant within the period of six months laid down in paragraph 1 of this Rule.

RULES OF PROCEDURE OF THE GOVERNING COUNCIL

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5. The selection of the Director of the Agency shall take place at a closed meeting of the Governing Council. The Governing Council shall elect a person by secret ballot from among the candidates proposed. If, in the first ballot, no candidate obtains the majority, additional ballots shall be taken and the candidate who obtains the least number of votes shall be eliminated at each ballot. If the number of candidates is reduced to two and there is a tie between these two candidates after three further ballots, the procedure established by this paragraph shall be recommenced. In this event the Governing Council may propose additional candidates.
6. The name of the person so selected shall be submitted to the Director-General of the World Health Organization to permit him to effect the appointment on such terms as the Governing Council may determine. The term of office of the Director of the International Agency for Research on Cancer shall be five years, and he or she shall be eligible for reappointment once only.

PROGRAMME, BUDGET AND FINANCE

*Rule 47*

The Governing Council shall:

- (a) review the programme of permanent activities, approve any special project and decide upon any supplementary programme;
- (b) consider the report of the Director of the Agency on the development of the programme and the scientific activities of the Agency;
- (c) adopt the budget authorizing expenditure for the next budgetary period after consideration of the budget estimates prepared by the Director of the Agency and the Scientific Council's recommendations on the programme;
- (d) consider and approve supplementary estimates for the current budgetary period if and as necessary;
- (e) examine the report of the auditor on the annual accounts of receipts and expenditures for the preceding financial year and take such action thereon as may be appropriate;
- (f) consider the report of the Director of the Agency on the payment of the contributions of Participating States.

*Rule 48*

No proposal for a review of the annual contributions of Participating States under Article VIII, paragraph 4, of the Statute of the Agency shall be placed on the agenda unless it has been communicated to Participating States at least ninety days before the opening of the session.

*Rule 49*

Except in so far as there is an express provision to the contrary in the Financial Regulations of the Agency, the procedure for the consideration of financial matters shall be governed by these Rules.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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ADMISSION OF NEW PARTICIPATING STATES

*Rule 50*

Applications made by Members of the World Health Organization for admission as Participating States in the Agency shall be addressed to the Director-General and shall be transmitted immediately to Participating States and the Director of the Agency.

Any such application shall be placed on the agenda of the next session of the Governing Council provided the application reaches the Director-General at least ninety days before the opening of such session.

*Rule 51*

The approval by the Governing Council of any request for admission as a Participating State shall be immediately communicated to the State which has submitted it. Such state, in accordance with Article XII of the Statute of the Agency, may then give the undertaking referred to in Article III of the Statute of the Agency by means of a formal notification addressed to the Director-General and shall become a Participating State from the date of the receipt of such notification by the Director-General.

SUSPENSION AND AMENDMENT OF RULES OF PROCEDURE

*Rule 52*

Subject to the provisions of the Statute of the Agency, any of the foregoing Rules may be suspended provided that at least forty-eight hours' notice of the proposal for such suspension has been given to the Chairman and communicated by him to the representatives twenty-four hours before the meeting at which the proposal is to be submitted. If, however, on the advice of the Chairman, the Governing Council is unanimously in favour of such a proposal, it may adopt it immediately and without notice.

*Rule 53*

Amendments of these Rules may be adopted by the Governing Council provided that notice of a proposed amendment is given in writing to Participating States or their representatives at least thirty days before the meeting at which the proposal is to be submitted.

GENERAL PROVISIONS

*Rule 54*

The Governing Council may at its discretion apply such Rules of Procedure of the World Health Assembly as it may deem appropriate to particular circumstances for which provision does not exist in these Rules.

RULES OF PROCEDURE OF THE SCIENTIFIC COUNCIL

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**RULES OF PROCEDURE OF THE SCIENTIFIC COUNCIL  
OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER<sup>5</sup>**

SESSIONS

*Rule 1*

The Scientific Council shall hold sessions at least once a year and as often as necessary by notice sent by the Director of the Agency to its members and to the Director-General of the World Health Organization. At least eight weeks' notice shall be given before the date of the opening of the session, unless a matter of great urgency is involved.

*Rule 2*

The Director of the Agency shall also convene the Scientific Council at the request of one-third of its members provided that the Agency has sufficient financial provision for so doing and that the Director judges that he cannot meet the wishes of the Scientific Council satisfactorily other than through the holding of an additional meeting. The request shall be addressed to him in writing and shall state the reason for the request. Subject to the foregoing the Scientific Council shall be convened within thirty days following receipt of the request. The agenda of such a session shall be limited to the questions having necessitated that session.

*Rule 3*

The meetings of the Scientific Council shall be held in private unless the Scientific Council decides otherwise.

AGENDA

*Rule 4*

The provisional agenda of each session shall be drawn up by the Director of the Agency after consultation with the Chairman. It shall be despatched with the notice of convocation sent in accordance with Rule 1.

*Rule 5*

Except in the case of sessions convened under Rule 2, the provisional agenda of each session shall include, *inter alia*:

- (a) all items the inclusion of which has been prescribed by the Scientific Council at a previous session;
- (b) any item proposed by the Governing Council;
- (c) any item proposed by a Participating State or the Director-General;
- (d) any item proposed by a member of the Scientific Council;
- (e) any item proposed by the Director of the Agency.

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<sup>5</sup> Text approved by the Scientific Council in April 1966 and amended in February 1967.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Rule 6*

The Director of the Agency may, in consultation with the Chairman, include any question suitable for the agenda which may arise between the despatch of the provisional agenda and the opening day of the session in a supplementary agenda which the Scientific Council shall examine together with the provisional agenda.

OFFICERS

*Rule 7*

The Scientific Council shall elect at the end of each session a Chairman and a Vice-Chairman from among its members. These officers shall hold office until their successors are elected. A rapporteur may be appointed at each session.

SECRETARIAT

*Rule 8*

The Director of the Agency shall be *ex officio* the Secretary of the Scientific Council and of any of its committees or working groups. He may delegate these functions.

*Rule 9*

The Secretariat shall, if necessary, prepare summary records of the meetings in the working languages and shall distribute them to the members of the Scientific Council as soon as possible after the close of the meeting to which they relate.

LANGUAGES

*Rule 10*

The working languages of the Scientific Council shall be English and French. Speeches made in Spanish or Russian shall be interpreted into both working languages; speeches made in either of the working languages shall be interpreted into the other working language and into Spanish and Russian.

CONDUCT OF BUSINESS

*Rule 11*

A majority of the members of the Scientific Council shall constitute a quorum.

*Rule 12*

The Rules of Procedure of the Governing Council concerning the powers of the Chairman and the conduct of the business shall apply *mutatis mutandis* to the Scientific Council.

RULES OF PROCEDURE OF THE SCIENTIFIC COUNCIL

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VOTING

*Rule 13*

(a) **Scientific questions**

Purely scientific questions shall not be submitted to a vote. If the members of the Scientific Council cannot agree, each shall be entitled to express his personal opinion and to state the reasons therefore in an individual or group report.

(b) **Other questions**

Questions which are not purely scientific may be submitted to a vote which shall follow the same procedure as that laid down in the Rules of Procedure of the Governing Council.

SUSPENSION AND AMENDMENT OF RULES OF PROCEDURE

*Rule 14*

Subject to the provisions of the Statute of the Agency the Scientific Council may decide to suspend the application of any of the foregoing Rules provided that at least 24 hours' notice of the proposal for such suspension has been given to its members or that the Scientific Council is unanimously in favour of such a proposal.

*Rule 15*

The Scientific Council may amend these Rules in the course of a session provided that notice of a proposed amendment is given in writing to its members at least eight weeks before the meeting at which the proposal is to be submitted.

GENERAL PROVISIONS

*Rule 16*

In addition to the cases provided for elsewhere by these Rules, the Scientific Council may at its discretion apply such Rules of Procedure of the Governing Council as it may deem appropriate to particular circumstances for which provision does not exist in the Rules of Procedure of the Scientific Council.

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FINANCIAL REGULATIONS

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**FINANCIAL REGULATIONS OF  
THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER<sup>6</sup>**

*Article I – Applicability*

1.1 The Regulations shall govern the financial administration of the International Agency for Research on Cancer (hereinafter referred to as the “Agency”).

*Article II – Applicability of the Financial Regulations of the  
World Health Organization*

2.1 The Financial Regulations of the World Health Organization shall govern the financial policies, practices and administration of the Agency except as provided in the Statute and in the following Articles.

*Article III – The Budget*

3.1 The Director of the Agency (hereinafter referred to as the “Director”) shall prepare the programme and the budget estimates covering the programme of permanent activities; the Director may also prepare supplementary programmes and special projects and the cost estimates and method of financing relating to such supplementary programmes and any special projects. The programme and budget estimates covering the permanent activities and the cost estimates regarding any supplementary programme or any special project shall be prepared in the manner prescribed by the Governing Council and shall be accompanied by such information, annexes or explanatory statements as the Director may deem necessary. The budget estimates shall be presented in euros.

3.2 All programme and budget estimates relating to the permanent activities, to supplementary programmes or special projects shall be submitted by the Director to the Scientific Council which shall consider their programme aspects and submit its recommendations thereon to the Governing Council through the Director. This material shall be submitted to the Scientific Council in sufficient time to permit transmission by the Director of its recommendations together with all appropriate documentation to reach each Participating State and the Director-General of WHO at least thirty days before the meeting of the Governing Council at which the budget is to be considered.

3.3 The Director of the Agency shall be authorized to transfer credits between sections of the budget subject to such conditions as the Governing Council may determine.

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<sup>6</sup> Text adopted by the Governing Council at its first session (23–24 September 1965) and amended at its Thirteenth, Fifteenth, Nineteenth, Thirty-Eighth, Forty-Third, Forty-Eighth, Fifty-Third, Fifty-Fourth and Fifty-Sixth sessions (resolutions GC/13/R3, GC/15/R5, GC/19/R6, GC/38/R8, GC/43/R7, GC/48/R6, GC/53/R8, GC/54/R7 and GC/56/R5).

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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*Article IV – Provision of Funds*

4.1 The appropriations for the administrative services and permanent activities of the Agency shall be financed by the annual contributions of each Participating State. These contributions shall be assessed in euros.

4.2 The annual contributions shall be due on the first day of January of each year and must be paid not later than 31 December of that year; any Participating State which has not paid its contribution by that date shall be considered to be in arrears.

4.3 New Participating States admitted under the provisions of Article III of the Statute shall be required to pay one third of a full contribution in the first year of membership from which the amount due to the Working Capital Fund shall be appropriated, two thirds of a full contribution in the second year of membership and 100% of a full contribution in the third and following years of membership.

*Article V – Funds*

5.1 There shall be established a General Fund for the purpose of accounting for the expenditures of the Agency. The contributions paid by members under Regulation 4.1 and any advances from the Working Capital Fund to finance general expenditures shall be credited to the General Fund.

5.2 There shall be established a Working Capital Fund in an amount and for purposes to be determined from time to time by the Governing Council. The source of moneys of the Working Capital Fund shall be the amounts appropriated from the contributions of Participating States or sums transferred from the Governing Council Special Fund. The amounts to be appropriated or transferred shall be determined by the Governing Council.

5.3 Pending the receipt of statutory annual contributions to the budget, appropriations may be temporarily financed from the Working Capital Fund or, if the cash balance of the Working Capital Fund is inadequate, by internal borrowing from other available cash resources of the Agency, excluding Trust Funds. The source of such interim financing shall be reimbursed as soon as and to the extent that income is available for that purpose. Any balances of internal loans outstanding at the end of the financial period shall be reported to the Governing Council.

5.4 Income from investments of the Working Capital Fund shall be credited to miscellaneous income.

5.5 There shall be established a Governing Council Special Fund to which shall be credited any budgetary surpluses, the unbudgeted contributions of new Participating States and miscellaneous income. The cash balances of this account as at 31 December of each year shall be used for purposes to be decided by the Governing Council from time to time by a two-thirds majority of its members who are representatives of Participating States.

FINANCIAL REGULATIONS

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5.6 In accordance with Article VIII, paragraph 7, of the Statute, the Governing Council may accept grants or special contributions from any individual, body or government. Where such grants or special contributions are specifically earmarked by the donor for financing a special project or projects, the Governing Council shall decide on acceptance after having received the advice of the Scientific Council. Such funds shall be accounted for separately. The interest earned on such funds will be credited to miscellaneous income.

*Article VI – Financial Statements and Audit*

6.1 Financial statements shall be prepared annually in accordance with International Public Sector Accounting Standards, together with such other information as may be necessary to indicate the current financial position of the Agency. The report shall be submitted annually for the approval of the Governing Council. The financial statements shall be presented in euros. The accounting records may, however, be kept in such currencies as the Director, IARC may deem necessary.

6.2 Audits of the accounts of the Agency shall be carried out by the internal as well as external auditors of the World Health Organization in accordance with their respective terms of reference. The external auditor shall report to the Governing Council on the annual accounts.

*Article VII – General Provisions*

7.1 These Regulations shall be effective as of the date of their approval by the Governing Council, and may be amended only by the Governing Council.

7.2 The Financial Rules of the World Health Organization shall be applicable to the financial and budgetary operations of the Agency, except as modified by the Statute or the Financial Regulations of the Agency. Any exceptions which may be necessary to meet the requirements of the Agency shall be subject to the approval of the Governing Council.

7.3 A Participating State which withdraws from participation in the operation of the Agency under the provisions of Article XIII of the Statute shall be required to pay the full amount of its contributions up to and including the year in which the withdrawal becomes effective.

## INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

**Appendix 1****PARTICIPATING STATES OF THE  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER  
(as at 13 May 2015)**

	<b>Effective date of membership</b>
Australia .....	23 September 1965
Austria .....	16 May 2008
Belgium .....	19 October 1970
Brazil .....	16 May 2013
Canada .....	1 January 1982
Denmark .....	4 May 1990
Finland .....	29 April 1986
France .....	15 September 1965
Germany .....	15 September 1965
India .....	18 May 2006
Ireland .....	10 May 2007
Italy .....	15 September 1965
Japan .....	12 May 1972
Morocco .....	13 May 2015
Netherlands .....	27 April 1967
Norway .....	29 April 1987
Qatar .....	16 May 2013
Republic of Korea.....	18 May 2006
Russian Federation .....	23 September 1965
Spain .....	15 May 2003
Sweden .....	3 May 1979
Switzerland .....	4 May 1990
Turkey .....	13 May 2011
United Kingdom of Great Britain and Northern Ireland .....	15 September 1965
United States of America .....	15 September 1965



# PREAMBLE

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The Preamble to the IARC Monographs describes the objective and scope of the programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a Monograph or list of evaluations.

## A. GENERAL PRINCIPLES AND PROCEDURES

### 1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended ‘... that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.’ The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation

of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase ‘of chemicals’ was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 ([Stewart & Kleihues, 2003](#)). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups ([IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991](#); [Vainio et al., 1992](#); [IARC, 2005, 2006](#)).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

## 2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term ‘agent’ refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand

as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer ‘hazard’ is an agent that is capable of causing cancer under some circumstances, while a cancer ‘risk’ is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word ‘risks’ in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed ‘carcinogenic’ if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms ‘neoplasm’ and ‘tumour’ are used interchangeably.

The Preamble continues the previous usage of the phrase ‘strength of evidence’ as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation ([IARC, 1991](#); [Vainio et al., 1992](#); [IARC, 2005, 2006](#); see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

### 3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (<http://monographs.iarc.fr>). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

#### 4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

#### 5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

##### (a) *The Working Group*

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

##### (b) *Invited Specialists*

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair

or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) *Representatives of national and international health agencies*

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) *Observers with relevant scientific credentials*

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at IARC *Monographs* meetings (available at <http://monographs.iarc.fr>).

(e) *The IARC Secretariat*

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests

to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano et al., 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (<http://monographs.iarc.fr>) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

## 6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (<http://monographs.iarc.fr>) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare

preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

## B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data

Studies of cancer in humans

Studies of cancer in experimental animals  
 Mechanistic and other relevant data  
 Summary  
 Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

## 1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

### (a) *General information on the agent*

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in

which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

### (b) *Analysis and detection*

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

### (c) *Production and use*

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production,

which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

#### (d) *Occurrence and exposure*

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure

with date and place. For biological agents, the epidemiology of infection is described.

#### (e) *Regulations and guidelines*

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

## 2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

#### (a) *Types of study considered*

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case-control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case-control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in

particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; [IARC, 2004](#)).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case-control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

#### *(b) Quality of studies considered*

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies.

Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case-control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than

those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies ([Breslow & Day, 1980](#)) and for cohort studies ([Breslow & Day, 1987](#)).

### (c) *Meta-analyses and pooled analyses*

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the

individual studies (pooled analysis) ([Greenland, 1998](#)).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variables that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

### (d) *Temporal effects*

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and

time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) *Use of biomarkers in epidemiological studies*

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes ([IARC, 1991](#); [Vainio et al., 1992](#); [Toniolo et al., 1997](#); [Vineis et al., 1999](#); [Buffler et al., 2004](#)). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the

known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) *Criteria for causality*

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality ([Hill, 1965](#)). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of

multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

### 3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species ([Wilbourn et al., 1986](#); [Tomatis et al., 1989](#)). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans ([Vainio et al., 1995](#)). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. [OECD, 2002](#)).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

#### (a) *Qualitative aspects*

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence ([Huff et al., 1989](#)). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent

should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) *Quantitative aspects*

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart et al., 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) *Statistical analyses*

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980;

Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly

when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals ([Haseman et al., 1984](#); [Fung et al., 1996](#); [Greim et al., 2003](#)).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

#### 4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than

one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

##### (a) *Toxicokinetic data*

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose-response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

##### (b) *Data on mechanisms of carcinogenesis*

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

*(i) Changes in physiology*

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

*(ii) Functional changes at the cellular level*

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap-junction-mediated intercellular communication.

*(iii) Changes at the molecular level*

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily

described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis ([Vainio et al., 1992](#); [McGregor et al., 1999](#)). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap-junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published ([Montesano et al., 1986](#); [McGregor et al., 1999](#)).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) ([Vainio et al., 1992](#)). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere ([Montesano et al., 1986](#); [McGregor et al., 1999](#)).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. [Capen et al., 1999](#)).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as

surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

### (c) *Other data relevant to mechanisms*

A description is provided of any structure-activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) *Susceptibility data*

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) *Data on other adverse effects*

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

## 5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (<http://monographs.iarc.fr>).

(a) *Exposure data*

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) *Cancer in humans*

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) *Cancer in experimental animals*

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) *Mechanistic and other relevant data*

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

## 6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) *Carcinogenicity in humans*

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity:***

The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity:***

A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity:***

The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity:***

There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative

risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

**(b) *Carcinogenicity in experimental animals***

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity:***

The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two

or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity:***

The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity:***

The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity:***

Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) *Mechanistic and other relevant data*

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physico-chemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as ‘weak’, ‘moderate’ or ‘strong’. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and

experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) *Overall evaluation*

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

**Group 1: The agent is carcinogenic to humans.**

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

**Group 2.**

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

**Group 2A: The agent is probably carcinogenic to humans.**

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may

be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

**Group 2B: The agent is possibly carcinogenic to humans.**

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

**Group 3: The agent is not classifiable as to its carcinogenicity to humans.**

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed,

especially when exposures are widespread or the cancer data are consistent with differing interpretations.

#### **Group 4: The agent is probably not carcinogenic to humans.**

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

#### *(e) Rationale*

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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**State Statutes/Regulations Relying on IARC Evaluations for Identifying Carcinogens**

Alaska Statutes Annotated, tit.23, § 23.30.121(b)(3)(C)

Connecticut General Statutes Ann., tit. 10, § 10-217c

Illinois Compiled Statutes Ann., ch. 40, § 5/3-114.6(c)

Illinois Compiled Statutes Ann., ch. 105, § 135/3 (b), (c)

Illinois Compiled Statutes Ann., ch. 415, § 5/58.2

Illinois Admin. Code, tit. 35, § 232.320

Illinois Admin. Code, tit. 35, § 620.110

Illinois Admin. Code, tit. 35, § 742.200

Illinois Admin. Code, tit. 77, § 848.110

Indiana Code, tit. 5, § 742.200

Illinois Admin. Code, tit. 77, § 848.110

Indiana Code, tit. 5, § 5-10-15-6

Louisiana Revised Statutes, tit. 33, § 33:2011(B)

Missouri Statutes, ch. 87, § 87.006(2)

Nevada Revised Statutes, tit. 53, § 617.453(b)(1)

New Hampshire Revised Statutes., ch.281-a, § 281-A:17(II)

Oregon Revised Statutes Ann., tit. 36, § 453.205(3)

Oregon Administrative Rules Compilation, ch. 437, § 437-004-9860(2)

Tennessee Code Ann., tit. 68, § 68-131-303(5)

Texas Govt. Code, § 607.055(b)

Vermont Administrative Code, tit. 16, § 16-3-100 App.D.

Virginia Administrative Code, tit., 8, §20-530-10

Virginia Code Ann., § 65.2-402(c)

Washington Administrative Code, tit. 173, § 173-333-200

**HEYDENS, WILLIAM F [AG/1000]**

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**From:** Thomas Sorahan [T.M.SORAHAN@bham.ac.uk]  
**Sent:** Saturday, March 14, 2015 6:18 AM  
**To:** FARMER, DONNA R [AG/1000]; Strupp Christian; Mette K. Jensen  
**Cc:** HEYDENS, WILLIAM F [AG/1000]  
**Subject:** RE: EPA openly discussed IARC findings at a CLA meeting on Thursday

Dear Donna

I understand your concerns about early release of information. We can discuss the issues you raise in more detail on Monday, but here are some immediate responses.

I do know of instances where observers at IARC felt they had been treated rudely or brusquely at Monograph meetings. That was not the case for me at Vol 112. I found the Chair, sub-chairs and invited experts to be very friendly and prepared to respond to all comments I made. Indeed, I think questions the epi sub-panel asked me about my recent multiple myeloma paper (Sorahan, 2015) were instrumental in not having multiple myeloma included on the charge sheet.

In my opinion the meeting followed the IARC guidelines. Dr Kurt Straif, the Director of the Monographs programme, has an intimate knowledge of the IARC rules and insists these are followed.

As you say, there are background sections in the Monograph preambles and presumably on the IARC website as to how the IARC process is supposed to work. The recent EHP paper you have by Pearce et al (the 124 author effort) is also good for describing how things are supposed to work (about the only thing it is good for).

I suppose the main difference between IARC evaluations and most national agency guidelines is that IARC has nothing to say (directly) about potency and appropriate exposure limits.

As you know, the Working Group (WG) only has four choices for evaluating the human data (evidence of no carcinogenicity [in practice, protective effect], inadequate, limited, sufficient). The WG chose limited for NHL and glyphosate, but it is not clearly laid down what is the difference between the upper band of inadequate and the lower band of limited. As far as I can see, this is left to each WG to decide on its own.

These remarks are all confidential and I do not wish to be referenced in any document from your PA/PR people. But I am happy to assist in formulating statements that you may wish to make (eg "The company does not accept there is credible evidence that glyphosate use can cause NHL. Indeed in the single most important study into the health of pesticide applicators (the AHS) there is no excess of NHL in all applicators when compared to State cancer incidence rates, no excess in glyphosate users compared to non-users, and no trend of NHL increasing with extent of use"). I'm sure Elizabeth Delzell will be going into some detail in comparing the NHL findings from the case-control studies and from the AHS, in her proposed meta-analysis.

Tom

-----Original Message-----

From: FARMER, DONNA R [AG/1000] [mailto:donna.r.farmer@monsanto.com]

Sent: 14 March 2015 02:25

To: Thomas Sorahan; Strupp Christian; Mette K. Jensen

Cc: HEYDENS, WILLIAM F [AG/1000]

Subject: EPA openly discussed IARC findings at a CLA meeting on Thursday

Tom, Christian and Mette,

One of our colleagues was on a CLA call with other companies, EPA and PRMA for the Residue Experts Work Group at the DOW office yesterday. The EPA person opened the meeting by telling the group that an EPA Observer (Jess Rowland) was in the meeting, reported back to EPA Staff that IARC classified 3 pesticides as 2a and then he named diazinon, malathion and glyphosate. When asked by our colleague that it was our understanding that that information was under embargo wasn't that his understanding as well...he said he was not told to keep the information embargoed. The EPA person said the EPA is not IARC, he was providing this report, without comment. The subject was not on the agenda; he offered up without asking.

# **Proposal for Post-IARC Meeting Scientific Projects**

DRAFT

May 11, 2015

# Why do more?

- Severe stigma attached to Group 2A Classification
- Aaron Blair continues to defend work & exaggerate number of studies w/ association while ignoring AHS
- In response to our critique, can expect IARC to beef-up monograph as much as possible
- IARC plans to pool data globally in the future
  - Blair announced at meeting that he has already put together an unofficial work group to begin the process
  - North American Pooled Project (NAPP) already underway and early results reported in 2014
  - Believe this will be used to move pesticides to Group 1
- Provide additional support ('air cover') for future regulatory reviews
  - Broad EU review recently recommended by BfR
  - Other regulatory agencies stated they will review after Monograph publishes
- ASTDR evaluation
- Prop 65
- Litigation support

# Counter IARC's selective use of data and flawed analyses/conclusions on Epidemiology, Animal Bioassays, and Genotoxicity (Mode of Action); Prevent future adverse outcomes

## Possibilities:

- Conduct and Publish new Meta-analysis
- Publication on Animal Data Cited by IARC\**New*
- Publish updated AHS study data
- Publish WoE/Plausibility Paper
- Genetox/MOA

# New Meta-analysis

- **Project Description**

- Conduct proper meta-analysis to support the position that glyphosate is NOT associated with NHL and multiple myeloma
- Publish separately & can be used in overall WOE/Plausibility publication (below)
- Could be completed/published prior to IARC Monograph

- **Risk**

- None, since we have already done the analysis

- **Cost**

- \$32K plus any translation costs

[Timing – Donna checking w/ Exponent, but currently estimate 3-4 months to write plus 2+ months to get online publication]

# Publication on Animal Carcinogenicity Data

- **Project Description**

- Publication on Animal Data Noted by IARC as Evidence for Carcinogenicity
- Studies/Tumors Involved:
  - Mouse kidney tumors – subject of claims that Monsanto convinced EPA to change conclusions
  - Haemangiosarcoma in mice (Cheminova), pancreatic islet cell tumors in 2 rat studies (Monsanto) – multiple regulatory reviews conducted, including WHO/FAO
  - Publication on Initiation-promotion study with Roundup®
- Greim & 1or 2 other external authors?
- Could be completed/published prior to IARC Monograph
- Could we add Japan data (TAC, Mitsui (formerly Sankyo)? Would likely increase timeline

- **Cost**

- Majority of writing can be done by Monsanto, keeping OS\$ down

# AHS Collaboration

- **Project Description**
  - Submit proposal to AHS to collaborate on project to add last several 10 years of data & publish
  - Do with expert academicians – (e.g., Tom Sorahan, Tim Lash, David Coggin)
- **Risk – low**
  - We already know data is ‘negative’ through 2008/2009 (Freeman *et al*, 2009)
  - AHS certainly would have already published any “+”
  - Write stringent protocol ahead of time
  - ‘Seasoned’ rational experts would be doing the analysis not just post-docs from AHS who need to ‘make a mark’
- **Downside**
  - Longer term project – won’t get quick results
  - AHS Executive Committee may decline
    - Plan B -> FOI Request
- **Cost**
  - Total ~\$75K; initial cost to make proposal substantially less

# Overall WOE/Plausibility Publication

## Possibly via Expert Panel Concept

- **Project Description**
  - Publish comprehensive evaluation of carcinogenic potential by credible scientists
- **Possible Panelists/Authors**
  - Solomon? (Exposure), Sorahan (Epidemiology), Greim? (Animal bioassay), G. Williams, Kirkland? (Genetox/MOA), Sir Colin Barry, Jerry Rice (ex-IARC head)
- **Cost**
  - \$200 – 250 K, depending on:
    - Who/how many scientists we include
    - How much writing can be done by Monsanto scientists to help keep costs down
  - Alternative: 1 or 2 separate publications w/ subset of authors?

# Genetox / MOA

- Counter IARC's claim of strong evidence of DNA damage/oxidative stress
- Could be important for future litigation support
- Gary Williams (NY Medical College) - Use gene expression to firm-up non-genotoxic MOA in positive *in vitro* studies with formulations
- Contact Rich Irons?

# Feedback

## Conduct and Publish new Meta-analysis

- **Legal** – value not apparent
- **RPSA** – ‘No-Brainer’
- **CE** – Makes sense; have pre-release and/or present at scientific meeting before publication; RPSA needs to work on explaining to public
- **Brussels RA** – clear value; get out before IARC Monograph

## Publish updated AHS study data

- **Legal** – most appealing; MON somewhat distanced & AHS involved
- **RPSA** – ‘No Brainer’; add 2,4-D & dicamba?
- **CE** – Makes sense; have pre-release and/or present at scientific meeting before publication; RPSA needs to work on explaining to public
- **Brussels RA** – clear value; agree w/ RPSA; get out before IARCMonograph if possible (not likely)

# Feedback

## Publish WoE/Plausibility Paper

- **Legal** – Appealing; best if use big names; better if sponsored by some group
- **RPSA** – How helpful to regulators? Could we do totally independent?
- **CE** - If done, real value in having 3<sup>rd</sup> party manage process; add a couple MDs; work with Shawna to have a couple key stakeholders (e.g., GMA) watch/hear the proceedings & take back to their communities
- **Brussels RA** – less clear benefit; will it really ‘trump’ IARC in needed circles?

## Genetox/MOA

- **Legal** – cannot assess value
- **RPSA** – Need to address this; include household surfactants
- **CE** – no real comment
- **Brussels RA** – agree with RPSA; also finish Nik Hodges study

# Additional Suggestions from CE

- Get someone like Jerry Rice (ex-IARC) to publish paper on IARC
  - How it was formed, how it works, hasn't evolved over time, they are archaic and not needed now
- Exposure paper that shows how exposure is really, really low!
- Form Crop Protection Advisory Group?
  - Includes nutritionist, MDs along with traditional science groups; include a NGO?
  - Internal contacts = Mike Parish/ Matt Helms, Kelly Fleming, Cvance Crow, Janice Persons
- Communication Plans
  - Need to build in right plans for all steps/actions, including plan that works for millenials; start as early as possible

UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS

TOWN OF LEXINGTON, on behalf of itself )	
and all others similarly situated, )	
Plaintiff, )	
)	C.A. No. 12-CV-11645
v. )	
)	
PHARMACIA CORPORATION, )	
SOLUTIA INC., and )	
MONSANTO COMPANY, )	
Defendants. )	

**DEFENDANTS' OPPOSITION TO PLAINTIFF TOWN OF LEXINGTON'S MOTION TO EXCLUDE THE REPORT AND TESTIMONY OF PETER G. SHIELDS, M.D.**

Pharmacia LLC, Solutia Inc. and Monsanto Company (collectively “Pharmacia” for ease and convenience) oppose the Town of Lexington’s motion to exclude the testimony and report of Dr. Peter G. Shields M.D. Dr. Shields is an experienced and heralded oncologist and epidemiologist, with a particular focus on the causes of cancer. He has decades of PCB-specific testing and research experience, having published primary research as recently as 2014. His opinions demonstrate that there is no causal relationship between PCBs and cancer, a topic which Lexington has repeatedly raised since the inception of this case. Nonetheless, Lexington seeks to exclude Dr. Shields’ testimony as unreliable and irrelevant.

The gravamen of Lexington’s claims are directed at proving potential adverse human health effects from airborne molecules of polychlorinated biphenyls (which Lexington avers were a component part of the window caulk and sealant installed in the Joseph Estabrook Elementary School prior to 1960). Lexington presses “property damage” claims premised on the volatilization of PCB molecules into the school’s indoor air and migration to other substrate materials. Lexington has consistently averred that the presence airborne PCB molecules in

school indoor air at specific age dependent levels included in a September, 2009 federal EPA press release<sup>1</sup> was an essential element of its *prima facie* case.

Lexington alleges that Dr. Shields' testimony is unreliable because his opinions differ from those of the International Agency of Research on Cancer ("IARC"), his opinions are not based on animal studies, and he has not personally conducted any PCB research in the past two decades. Plaintiff Town of Lexington's Motion to Exclude the Report and Testimony of Peter G. Shields, M.D., Doc. 230 ("Lexington Motion") at 5-7. These contentions are riddled with holes and unsound logic. First and foremost, Lexington ignores Dr. Shields' expertise in epidemiology, which by definition focuses on the study of human populations. Second, Dr. Shields applied the Bradford Hill methodology, which remains the most appropriate and useful methodology to assess general causation. That his opinions may differ from one organization's findings does not render them suddenly unreliable. In addition, the statement by Lexington that Dr. Shields' opinions differ from IARC is preliminary; IARC has stated their reclassification for PCBs as a cause of malignant melanoma in 2013, but has not released their monograph setting forth their rationale. Dr. Shields explicitly stated he is waiting for that document. Finally, Dr. Shields has remained clinically active and continues to publish on the chemical and genetic causes of cancer. His opinions are based on a review of the scientific literature conducted from 1975 through 2014. Thus Dr. Shields' opinions take into account the current scientific literature on PCB's relation to cancer and carcinogenic agents in general.

Lexington also argues that Dr. Shields' opinions are not helpful in this case because "Lexington does not claim to have conducted PCB remediation because of fear of cancer". Lexington Motion at 7. This statement is belied by Lexington's own allegations in its

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<sup>1</sup> Public Health Levels of PCBs in School Indoor Air (ng/m3): (1) Age 1 -2; 70; (2) Age 2-3; 70; (3) Age 3-6; 100; (4) Age 6-12; 300; (5) Age 12-15; 450; (6) Age 15-19; 600; (7) Age 19+; 450.

Complaint: “PCBs are persistent environmental pollutants that have been demonstrated to cause cancer, as well as a variety of other adverse health effects. Children are particularly vulnerable to the toxic effects of PCBs.” Complaint, Doc. 1 at ¶ 2. Even now, Lexington continues to inject the “toxic” and “carcinogenic” effects of PCBs into this litigation through its “rebuttal” experts. So, while Lexington plans to pursue scaremongering over alleged adverse health effects to “the children,”<sup>2</sup> it seeks to prevent Pharmacia from delivering established scientific facts to the jury. Thus, Dr. Shields’ opinions are not only relevant but necessary to prevent Lexington from unduly prejudicing the jury with its bare assertions and statements unsupported by science.

As such, the Court should deny Lexington’s motion in full.

#### STATEMENT OF FACTS

In September 2012, Lexington filed the present product liability suit against Pharmacia, alleging PCBs were defective “in design” and that Pharmacia failed to properly warn and instruct about its products. While Lexington maintained that this was a property damage claim, it spent not less than eight full paragraphs describing “PCB toxicity”. Complaint, Doc. 1 at ¶¶ 18-25. Among its allegedly toxic characteristics, Lexington alleged that the EPA, the International Agency for Research on Cancer, the National Toxicity Program and the National Institute for Occupational Safety and Health had each classified PCB as a “probable human carcinogen.” Complaint, Doc. 1 at ¶ 19. Throughout the litigation, Lexington continued to emphasize the harmful health effects of PCBs.

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<sup>2</sup> For example, Lexington represented to the Court that “The demolition of that building is currently scheduled so as to protect, to the maximum extent possible, the health and welfare of the 500 children who attend the school.” Plaintiff Town of Lexington’s Motion for a Protective Order Regarding Inspection of the Estabrook Elementary School. Doc. 69. “To comply with the EPA mandate, provide a healthy educational environment for Estabrook students, and promote public safety, Lexington must commence demolition of the contaminated building in March 2014.” “[D]elaying demolition of the building would impose on Lexington and the hundreds of schoolchildren who would be forced to attend school in the continued presence of a hazardous building. ...” Plaintiff Town of Lexington’s Memorandum or Reasons in Support of Motion for Protective Order Regarding Inspection of the Estabrook Elementary School at 1-2. Doc.70.

On November 14, 2014, Pharmacia timely produced a comprehensively authored report by Dr. Peter G. Shields, an epidemiologist and oncologist, to address Lexington's allegations that PCBs were a known human carcinogen. Expert Report Peter G. Shields, MD, November 14, 2014 (Updated 2/11/15 to reflect correction of headers) ("Shields Report"), attached as Exhibit A. The report was 115 pages with 416 article citations about the causes of cancer generally and PCBs in particular. It includes all, or almost all of the primary research ever published about PCBs and cancer. Dr. Shields graduated from the University of Pennsylvania in 1979 with a B.A. in Biochemistry and American Civilization. He went on to receive his M.D. in 1983 from Mount Sinai School of Medicine. Shields Report, Curriculum Vitae. Dr. Shields is currently a tenured Professor at Ohio State University's Department of Internal Medicine in the College of Medicine, and in the Department of Epidemiology at the College of Public Health. Shields Report at 5. Dr. Shields has authored several primary studies and review articles about PCBs from 1990 to 2006, including positive results when they occurred, and then decided temporarily to no longer pursue PCB research because of his belief that PCBs were not a measurable cause of cancer. In 2014, however, he again published on the topic, because he had the opportunity to consider PCB health effects in a new and better way. That paper failed to show an increased risk of cancer in humans, even among the most highly exposed in an occupational setting.

Dr. Shields offered six major conclusions in his report. Shields Report at 3-4.

- PCBs are not causally related to the development of cancer in humans;
- Epidemiology studies demonstrate that the rates of cancer mortality in workers with high levels of exposure to PCBs are not statistically increased;
- IARC's recent re-classification of PCBs as a known human carcinogen is only known as a news report. IARC's process for classification, includes publishing an extensive

monograph detailing their methodology and their conclusions with a literature review. This has not yet been released. Importantly, IARC considered all other cancers and concluded that there was not sufficient evidence for PCBs as a human carcinogen. At deposition, Dr. Shields stated he was waiting for the IARC monograph before he could formulate any opinions about its classification of PCBs. The classification by IARC, according to the news report, was based on occupational studies with exposures that were orders of magnitude higher than possible for Lexington's school occupants. In any event, Dr. Shields noted in his report on page 10 "It is important to note that a known human carcinogen classified by IARC should not be equated with a conclusion that it will cause cancer in humans." Shields Report at 10;

- The general population is exposed to PCBs through diet;
- The dose-response relationship of exposure to disease is a fundamental concept for toxicology, while consistency among studies is a fundamental concept for epidemiology. The two of these together, considering studies of the most highly exposed PCB workers provides substantial reassurance to the general population for no increased risk;
- The EPA's suggested indoor air levels have a high margin of safety and exceeding those levels does not actually increase the risk of cancer; and
- Exposure to PCBs at very low doses cannot be assumed to increase the risk of cancer.

Dr. Shields was deposed on February 13, 2015. Deposition of Peter G. Shields, February 13, 2015, ("Shields Depo.") attached as Exhibit B. Lexington now moves to exclude all of Dr. Shields opinions and testimony.

## ARGUMENT

### **I. Dr. Shields's Opinions Are Reliable**

Lexington argues that Dr. Shields's opinions are unreliable because they do not conform to IARC's findings, they are not derived from animal studies, they are not based on his personal research, and they were formed solely for the purposes of litigation. As discussed more fully below, these arguments are not a proper measure of reliability, and are simply false and a misrepresentation of his opinions and testimony. Dr. Shields's opinions employ "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field", *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999), and are thus not only reliable but admissible.

**A. Dr. Shields' Disagreement With The Conclusions Reached By IARC Is Not Indicative Of A Poor Methodology**

Lexington argues that Dr. Shields's opinions are unreliable because they run contrary to one organization, the International Agency for Research on Cancer ("IARC"), and, incidentally Lexington's own "rebuttal" expert, Dr. Pessah. Mere disagreement alone, however, is insufficient to find an expert's opinions unreliable, particularly where the testimony in question is founded on a rigorous and tested methodology. *See Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 85 (1st Cir. 1998).

When scrutinizing potential experts, the "focus must be solely on principles and methodology, not on the conclusions that they generate." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 580 (1993). As such, "*Daubert* does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct." *Ruiz-Troche*, 161 F.3d at 85. Rather, the proponent must only show that the expert's conclusions were "arrived at in a scientifically sound and methodologically reliable fashion." *Id.*

To reach his opinions, Dr. Shields' applied a well-established practice for considering whether a chemical can cause cancers. Shields Report at 9. Specifically, Dr. Shields applied the Bradford-Hill methodology to assess causation, which, incidentally, is the same methodology

used by IARC. Shields Report at 10. The Bradford-Hill criteria were published in 1965 and have been in regular use since then, including by agencies such as IARC and the U.S. Department of Health and Human Services, for example, in Surgeon General's many reports on smoking. Dr. Shields and others have specifically published on the use of the Bradford-Hill criteria and PCBs (Shields 2006; Golden 2009; Golden 2003). Next, Dr. Shields applied the Bradford Hill guidelines to his meticulous review of over 300 human and animal studies on PCBs. Shields Report at 13-76. Dr. Shields concluded that, under the Bradford-Hill guidelines, there was no causal relationship between PCBs and all cancers and specific cancers: non-Hodgkin lymphoma, breast cancer, prostate cancer, colon cancer, liver cancer, lung cancer, sarcoma, pancreas cancer, or even melanoma. Shields Report 25-58. Dr. Shields provides over 400 citations throughout his report, confirming again and again that his conclusions are shared by scientists, oncologists, and professional communities.

Regarding his disagreement with IARC's conclusions, Dr. Shields makes two points: first, IARC's designation of PCBs as carcinogenic is limited to melanoma and cannot be extrapolated to other types of cancers, Shields Report at 13; second, the scientific literature does not support IARC's conclusion that there is a melanoma risk from PCBs, Shields Report at 44. IARC's statement has only been released preliminarily and relates to only one type of cancer, namely malignant melanoma. Where IARC considered all other types of cancer, it concluded that there is no sufficient evidence in humans to consider PCBs a known human carcinogen. Until the rationale and data for IARC's melanoma determination is released (now overdue by 2 years), it is unclear whether or not the Working Group opinions relate to Lexington in any way. Importantly, the IARC process and opinions are clear that its classifications should **not** be used

to opine that PCBs will cause cancer in humans. Thus, whether or not Dr. Shields disagrees with IARC, the views of this one agency does not make Dr. Shields' opinions unreliable.

It is well established that different scientists can use the same data and research to reach different, but equally admissible conclusions. "That two different experts reach opposing conclusions from the same information does not render their opinions inadmissible." *Walker v. Soo Line R. Co.*, 208 F.3d 581, 589 (7th Cir. 2000); *see also Hines v. Consol. Rail Corp.*, 926 F.2d 262, 274 (3d Cir. 1991); *Allapattah Servs., Inc. v. Exxon Corp.*, 61 F. Supp. 2d 1335, 1341 (S.D. Fla. 1999) ("Merely because two qualified experts reach directly opposite conclusions using similar, if not identical, data bases, or disagree over which data to use or the manner in which the data should be evaluated, does not necessarily mean that, under *Daubert*, one opinion is *per se* unreliable."). Given Dr. Shields's well-reasoned analysis, Lexington's assertions that Dr. Shields's opinions are somehow unreliable because he does not agree with IARC's conclusions are unpersuasive.

Finally, contrary to the Lexington's suggestions, Dr. Shields adequately identified at least three other scientific organizations which similarly refused to classify PCBs as a human carcinogen.<sup>3</sup> *See* Shields Report, Table 2 at 15. For example, the EPA and American Council of Governmental Industrial Hygienists only confirmed PCBs as an animal carcinogen. NIOSH and OSHA only classified PCBs as a carcinogen with no further categorization. Shields Report, Table 2 at 15.

**B. Dr. Shields Is An Epidemiologist And Accordingly His Expert Opinion Is Based On Human Testing And Data**

Lexington contends that Dr. Shields's opinions are unreliable because his opinions are not based on animal PCB studies. Lexington Motion at 6. Lexington somehow supports its

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<sup>3</sup> As Lexington points out, Dr. Shields already agreed that PCBs can cause cancer in animals. Shields Dep. at 88. However chemicals that are carcinogenic to animals are not necessarily carcinogenic for humans.

argument by quoting from Pharmacia's toxicology expert, James Lamb, Ph.D., who relied on animal studies in his toxicological analysis. Lamb Depo. at 64, excerpts attached as Exhibit C. Lexington, however, fails to consider the differences between epidemiology and toxicology. As Dr. Shields stated in his report and at deposition, animal studies are not useful for making conclusions that PCBs *will* cause cancer in humans, rather they are used as a screening test for chemical exposures to assess what *may* cause cancer in humans. They are also used to understand how cancer mechanisms are affected by chemicals, but only when the similar mechanisms exist in the experimental animal model and humans. This often is not the case because the screening animal studies are designed to provide a positive result. The conclusion that a chemical *will* cause cancer in humans can only come from adequate human study, specifically through epidemiology. Shields Report at 9, 24; Shields Depo. at 121.

While toxicology and epidemiology are interrelated, they are still considered separate fields of study and expertise, each with its own methods, data points, and review. Toxicology is the study of "hazards or safety of chemicals" whether in humans or animals. Lamb Depo. at 7-8. Epidemiology, on the other hand, is the specific study of diseases, including their incidence, mortality, and risks in a *specific population*. Lamb Depo. at 8; Shields Depo. at 29.

Q. And what is epidemiology?

A. It's the study of disease and causes of the disease in populations.

\* \* \*

A. Epidemiology is studying disease incidence, mortality, and in my case risks.

Q. How about toxicology? What is that?

A. Well, toxicology is a different specialty with overlap to epidemiology. That tries to understand the toxic effects in biological systems, including people. So toxicology includes laboratory tests and cell cultures, animal studies, but also humans.

Q. Are laboratory tests and cell cultures techniques used by epidemiologists?

A. Generally not. You know, there's some overlap. So in my research activities, I run a laboratory; and to better understand the causes of cancer in people, we will do ... toxicology testing in the laboratory and then I apply it to the epidemiology. So there's a spectrum there.

Shields Depo. at 28-30.

Q. What is the difference between toxicology and epidemiology?

A. Epidemiology is more the study of human diseases; whereas toxicology is more the study of how chemicals cause harm, whether in humans or in animals. Epidemiologists study human populations; whereas I evaluate data on how a chemical causes harm.

Lamb Depo. at 8.

Dr. Shields does not consider himself a toxicologist. Shields Depo. at 31.

As to the animal studies, Dr. Shields explained that he did not place as much value on animal studies as human studies for multiple reasons.

Among the types of data that should be evaluated, human epidemiological data is substantially more reliable than laboratory *in vitro* and experimental animal data, assuming the epidemiological and other human studies are of good quality. If there is sufficient epidemiological data to make a conclusion, then experimental animal or other studies are sometimes considered only in the context of understanding biological mechanisms.

Shields Report at 9. In addition, there are pathological dissimilarities between humans and animals and the methodologies used in animal studies “reduces confidence in extrapolating such to human cancer risk, such as high dose exposures and the maximally tolerated dose.” Shields Report at 24. Dr. Shields explained that he did not have to rely on animal studies when he “had a large number of epidemiologic studies in people that trump animal studies.” Shields Depo. at 121.

Finally, the EPA’s reliance on PCB animal studies is driven out of “cautionary” concerns. Shields Report at 14. In fact, Dr. Shields explains that “these agency methods and findings are not appropriate to support a conclusion of cancer causation in a particular individual, or to predict risk in particular individuals, or to conclude whether the chemical is carcinogenic in humans at all.” Shields Report at 14. The EPA is tasked with setting up precautionary measures to avoid any potential harm, while scientists like Dr. Shields are tasked with finding the precise

causes of cancer. These are very separate goals, and as such, different data sets will have different levels of relevance.

### **C. Dr. Shields's Opinions Are Based On Recent Studies Of PCBs**

Lexington contends that Dr. Shields's opinions are unreliable because he has not studied PCBs for approximately twenty years. Lexington Motion at 6. Lexington argues that Dr. Shields' lack of recent PCB research somehow renders his opinions out of touch with the current science and that the science changed in the past 20 years. Lexington Motion at 7.

First and foremost, Lexington's assertion that Dr. Shields has not studied PCBs for approximately twenty years is patently untrue. As Lexington admits in a footnote, although Dr. Shields' initial PCB research occurred in the 1990s, he published a PCB-related study just last year. Lexington Motion at 7, n. 6; Shields Depo. at 45. This article, which studied employees exposed to PCBs leaking from capacitors, required a direct study of PCBs and their potential effects on human health, and provided further support for Dr. Shields's already well-established opinions. Shields Depo. at 48, 50. After analyzing the data collected in the 2014 study, Dr. Shields concluded that despite the workers' incredibly high exposure, there still "really wasn't any clear increased cancer risk." Shields Depo. at 50. This conclusion aligned seamlessly with the conclusions from his original research in the 1990s. Shields Depo. at 44-45.

Second, it is clear from Dr. Shields's 2014 study that, regardless when the research was conducted, the results remain the same – there is simply not enough evidence to find a causal connection between PCBs and cancer. As Dr. Shields explains, he believes that his study of PCBs and cancer is a "dead issue." Shields Depo. at 123. "[O]nce it became clear that PCBs were not a cause of cancer, there was no point of doing any more studying." Shields Depo. at 44-45. The 2014 study represented a new opportunity for Dr. Shields to study PCBs and health

effects in a different way, only for him to find, yet again, that PCBs were not causing cancer in heavily exposed workers.

In addition, Dr. Shields also remains intimately familiar with the research performed in the past twenty years. Dr. Shields is a tenured Professor in the Departments of Internal Medicine in the College of Medicine and the Department of Epidemiology at the College of Public Health, and the Deputy Director of the Ohio State University Comprehensive Cancer Center. Shields Report at 5. In these positions, Dr. Shields is able to remain up to date and thoroughly connected to the leading theories on potential causes for cancer. Shields Depo. at 43-45. In fact, Dr. Shields cited not less than 235 studies published between 1994 and 2014 in reaching his conclusion. Shields Report, “Literature Cited”, at 77-115. Accordingly, Lexington’s allegation that Dr. Shields is somehow disconnected from the current scientific literature on PCBs is demonstrably false.

#### **D. Dr. Shields’ Opinions Were Not Generated Solely For Litigation**

Finally, Lexington argues that Dr. Shields’ opinions are unreliable because they were generated “solely for litigation purposes”. Lexington Motion at 1. However, Lexington provides zero factual support for this accusation. “That an expert testifies based on research he has conducted independent of the litigation provides important, objective proof that the research comports with the dictates of good science.” *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995). In addition, expert testimony which is “based directly on legitimate, preexisting research unrelated to the litigation provides the most persuasive basis for concluding that the opinions he expresses were derived by the scientific method.” *Id.*, 43 F.3d at 1317.

Dr. Shields’ opinions are based on his three decades of personal research and study, funded in-part through federal dollars, and his continuing familiarity with the scientific literature

conducted by others. As he explains in his report, Dr. Shields bases his opinions on a career of professional research into the causes of cancer and fostered by his continuing care of oncology patients. Shields Report at 5, 7. This is not the kind of litigation-entrenched opinion creation that federal courts have traditionally rejected. *See Lust By & Through Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 597 (9th Cir. 1996) (excluding testimony of a “professional Plaintiff’s witness” based on lack of professional standards in conducting research and generating opinion by conducting research in preparation for expert testimony in another case); *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) (excluding expert testimony because “none of the experts based his testimony on preexisting or independent research”); *Nat’l Bank of Commerce (of El Dorado, Ark.) v. Dow Chem. Co.*, 965 F. Supp. 1490, 1518 (E.D. Ark. 1996) (excluding expert testimony because litigation was the force in directing his research and expert had performed no research on the product in question independent of litigation). As such, Lexington’s assertion that Dr. Shields formed his opinions solely for litigation fails on its face.

**II. Dr. Shields’ Opinions Are Relevant Because Lexington Has Repeatedly Made The Potential Cancer-Causing Effects Of PCBs An Issue In This Litigation**

Lexington suggests that, despite dozens of its own motions, memoranda, and expert reports which claim that Lexington was forced to remove building materials because of potential negative health effects from PCBs, Dr. Shields’ expert opinions about the carcinogenic effects of PCBs does not “fit” into this litigation. Lexington Motion at 7. Not only is this proposition absurd, but it defies the very theory proposed by Lexington since the inception of this case.

Lexington repeatedly argued that it was forced to remove the building products because they caused a “threat to public health.” Complaint, Doc. 1 at ¶ 31.<sup>4</sup> Throughout the span of this

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<sup>4</sup> While Lexington alleged it suffered property damage, there was actually no structural damage to Estabrook, the building products themselves were fully functional, and no structural weaknesses occurred because of the PCBs.

almost three-year-old litigation, Lexington has maintained that PCBs are dangerous because they are carcinogenic, and thus require remediation:

PCBs are persistent environmental pollutants that have been demonstrated to cause cancer, as well as a variety of other adverse health effects. Children are particularly vulnerable to the toxic effects of PCBs. Complaint, Doc. 1 at ¶ 2.

Just as in the environment, PCBs accumulate in the human body. According to the EPA, PCBs have been demonstrated to cause cancer, as well as a variety of other adverse health effects on the immune, reproductive, nervous, and endocrine systems of animals and humans. Complaint, Doc. 1 at ¶ 18.

PCBs cause cancer and a variety of other serious adverse health effects, and children are particularly vulnerable to PCBs. Lexington's Opposition to Defendants' Motion to Dismiss, Doc. 26 at 16.

PCBs are classified as known human carcinogens by the International Agency for Research on Cancer. According to the U.S. Environmental Protection Agency ("EPA"), children exposed to PCBs can suffer damage to their immune, reproductive, memory and endocrine systems . . . The Town of Lexington ("Lexington") suffered a multi-million dollar injury when it was required by EPA guidelines to reduce concentrations of PCBs in the indoor air at Estabrook Elementary School. Memorandum in Support of Motion to Certify Class, Doc. 119 at 2.

This case concerns whether Massachusetts' children are attending schools in safe, healthy environments free from the presence of PCBs - a known human carcinogen. "PCBs are a toxic threat that should not be in any school." Reply in Response to the Motion to Certify the Class, Doc. 194 at 1.

Albeit untimely, Lexington now proffers "rebuttal" expert testimony to opine on this same issue:

I concur with the [IARC] that, when considering the 'weight of evidence' from biologically plausible mechanisms, results from animal studies, and several dozen epidemiological studies, there is sufficient evidence for the carcinogenicity of PCBs in humans, especially for developing melanoma.

Expert Report of Isaac Pessah at 4, attached as Exhibit D.

**Q:** "Is your basis for concluding that Dr. Shields' conclusions, with respect to positive associations reflect spurious results rather than an increased risk, is that based solely on your reading of the IARC assignment?"

- A. No. It's also based on my understanding that PCBs that are tumor promoters have an adverse outcome pathway that's been well defined, and that is one of my expertise."

Deposition of Isaac Pessah, April 8, 2015, attached as Exhibit E.

Lexington argues that Dr. Shields' opinions are irrelevant because they only address one of "myriad adverse health effects related to PCBs." Lexington Motion at 8. Yet, Lexington correctly points out that expert testimony may be relevant "not only in the sense that all evidence must be relevant, but also in the incremental sense that the expert's proposed opinion, if admitted, likely would assist the trier of fact to understand or determine a fact in issue." *Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 81 (1st Cir. 1998); see *Bricklayers & Trowel Trades Int'l Pension Fund v. Credit Suisse Sec. (USA) LLC*, 752 F.3d 82, 91 (1st Cir. 2014); *Clark v. Edison*, 881 F. Supp. 2d 192, 200 (D. Mass. 2012).

Here, Dr. Shields' opinions do not suddenly become irrelevant because he only addresses one aspect of Lexington's theory.<sup>5</sup> Quite the opposite, Dr. Shields' expert opinion will help guide the jury to determine a fact that Lexington caused to be at issue – whether PCBs are actually carcinogenic at the low doses present at Estabrook. This will help the jury determine if any potential adverse health effects from PCBs have any relationship whatsoever to Lexington's alleged property damage caused by volatilized PCB molecules from caulk and sealant installed in the Estabrook School more than 50 years ago.

Now, faced with an exceptionally qualified expert opining that PCBs are not causally connected to cancer, Lexington tries to dodge and weave its way out of the fanciful claim it created from whole cloth. The Court denied Lexington's motion to change its basic claims and legal theories in its March 24, 2015 order. Lexington framed the case that it must now prove.

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<sup>5</sup> Unlike Lexington, Pharmacia decided to address each asserted health effect by an expert in that respective field. See Expert Reports of Drs. Lamb, Starr, Schell, and Shields.

Pharmacia marshaled competent, admissible evidence to demonstrate that Lexington's claim is baseless.

Accordingly, the Court must deny Lexington's motion to exclude the opinions and testimony of Dr. Shields.

### III. CONCLUSION

For the reasons discussed above, Pharmacia requests that the Court deny Lexington's Motion to Exclude the Report and Testimony of Peter G. Shields, M.D.

Dated: May 14, 2015

Respectfully Submitted,

MONSANTO COMPANY,  
SOLUTIA INC., and  
PHARMACIA CORPORATION

By their attorneys,

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**CERTIFICATE OF SERVICE**

I HEREBY CERTIFY that on this 14th day of May, 2015, the foregoing document was filed electronically. Notice of this filing will be sent by e-mail to the following parties by operation of the Court's electronic filing system:

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/s/ Richard L. Campbell

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UNITED STATES DISTRICT COURT  
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP )  
PRODUCTS LIABILITY ) MDL No. 2741  
LITIGATION )  
\_\_\_\_\_ ) Case No.  
THIS DOCUMENT RELATES ) 16-md-02741-VC  
TO ALL CASES )

WEDNESDAY, JANUARY 11, 2017  
CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER  
- - -

Videotaped deposition of Donna Farmer, Ph.D., Volume I, held at the offices of HUSCH BLACKWELL, L.L.C., 190 Carondelet Plaza, Suite 600, St. Louis, Missouri, commencing at 9:04 a.m., on the above date, before Carrie A. Campbell, Registered Diplomat Reporter, Certified Realtime Reporter, Illinois, California & Texas Certified Shorthand Reporter, Missouri & Kansas Certified Court Reporter.

- - -  
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877.370.3377 ph | 917.591.5672 fax  
deps@golkow.com

1 your file, and I have a copy for you and a  
2 copy for counsel.

3 You've seen this before,  
4 haven't you, ma'am?

5 MR. JOHNSTON: Give her a  
6 second to look at it.

7 MR. MILLER: Of course.

8 QUESTIONS BY MR. MILLER:

9 Q. Take your time. Have you seen  
10 it before? Take your time.

11 MR. JOHNSTON: You didn't  
12 really give her a second to look at it.

13 MR. MILLER: Who's being  
14 argumentative?

15 QUESTIONS BY MR. MILLER:

16 Q. Let me know when you're ready.

17 All right, ma'am. Now this is  
18 a document, a copy of an e-mail, sent by you,  
19 right, ma'am? Donna Farmer?

20 A. Yes.

21 Q. Okay. And it was sent by you  
22 on September 21, 2009, right?

23 A. Yes.

24 Q. And it's concerning Roundup,  
25 right?

1 A. Yes.

2 Q. And in that you say this: "You  
3 cannot say that Roundup does not cause  
4 cancer. We have not done the carcinogenicity  
5 studies with Roundup."

6 Did I read that correctly?

7 A. Yes, you did read that  
8 correctly.

9 But I want to point out that I  
10 should have -- in other e-mails that I have  
11 done is that what we talk about is while we  
12 have not done carcinogenicity with Roundup  
13 per se, we have data on glyphosate. We don't  
14 believe the surfactants -- they are not  
15 carcinogenic.

16 So normally what I would say is  
17 that when you put those two together, even  
18 though we haven't done these carcinogenicity  
19 studies, that there is no evidence that  
20 Roundup would be carcinogenic.

21 Q. I want to read what you said  
22 before the lawsuit was filed.

23 You said, "You cannot say that  
24 Roundup does not cause cancer...we have not  
25 done carcinogenicity studies."

Message

**From:** FARMER, DONNA R [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=180070]  
**Sent:** 9/21/2009 5:12:07 PM  
**To:** COMBEST, JOHN C [AG/1000] [john.c.combest@Monsanto.com]  
**Subject:** RE: Roundup article in Fremantle Herald

I didn't find anything on the Australian site either ...however take this question 5. It is not Roundup that is taken up it is glyphosate. It stops the synthesis of 3 amino acids (they are used to make proteins) and this "process" is also found in microbes and fungi.

5. How does Roundup work?

Roundup is taken up through the leaves and moves in the sap flow throughout the plant. It stops the production of proteins so that the plant starves. This process is found only in plants; Roundup has extremely low toxicity to humans and wildlife.

Or this - you cannot say that Roundup does not cause cancer..we have not done carcinogenicity studies with "Roundup".

2. Will Roundup harm my family or me?

Based on the results of short term and long term testing, it can be concluded that Roundup poses no danger to human health when used according to label directions. In long term exposure studies of animals, Roundup did not cause cancer, birth defects or adverse reproductive changes at dose levels far in excess of likely exposure.

I will follow up with the Monsanto folks who interface with Scotts...they are aware that Scotts does these things.

Donna

-----Original Message-----

**From:** COMBEST, JOHN C [AG/1000]  
**Sent:** Monday, September 21, 2009 11:07 AM  
**To:** FARMER, DONNA R [AG/1000]  
**Subject:** RE: Roundup article in Fremantle Herald

I did not find any reference on their main (US) page to "biodegradable."

-----Original Message-----

**From:** FARMER, DONNA R [AG/1000]  
**Sent:** Monday, September 21, 2009 11:06 AM  
**To:** COMBEST, JOHN C [AG/1000]  
**Subject:** RE: Roundup article in Fremantle Herald

Did you find the link?

This is to their Q&A and I can tell you they have a number of things that a not acceptable.  
<http://www.scottsaustralia.com.au/FAQs/Roundup>

-----Original Message-----

**From:** COMBEST, JOHN C [AG/1000]  
**Sent:** Monday, September 21, 2009 8:11 AM  
**To:** PERSON, JANICE L [AG/1030]; FARMER, DONNA R [AG/1000]; HELSCHER, THOMAS M [AG/1000]  
**Subject:** Fw: Roundup article in Fremantle Herald

Janice and Donna,

Here's the Australian thread, to the latest message.

John

----- Original Message -----

**From:** LEADER, MICHAEL [AG/5020]  
**To:** ANDERSON, NEIL J [AG/5020]; MCNAUGHTON, HONI JANINE [AG/5020]; MCGREGOR, JOHN [AG/5020]; HELSCHER, THOMAS M [AG/1000]

Cc: MCLEAN, KERYN [AG/5020]; TAYLOR, IAN N [AG/5020]; ARMSTRONG, JANICE M [AG/5340]; COMBEST, JOHN C [AG/1000]

Sent: Mon Sep 21 00:08:56 2009

Subject: RE: Roundup article in Fremantle Herald

Thanks Neil. Honi has already have pointed out the flaws in the studies, but there can't be any harm in doing so again. Studies on the safety of Roundup is a good approach, but I believe there are also some on glyphosate's benefits for the environment (even if the surfactant is not biodegradable). It's a shame the Scott's guy is blaming us too!!

Cheers

Michael

Michael Leader

Corporate and Regulatory Affairs Lead, Australia/New Zealand

Level 12, 600 St Kilda Road; Melbourne VIC 3004

Email: michael.leader@monsanto.com

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<<http://www.monsanto.com.au/>>

From: ANDERSON, NEIL J [AG/5020]

Sent: Monday, September 21, 2009 12:39 PM

To: MCNAUGHTON, HONI JANINE [AG/5020]; MCGREGOR, JOHN [AG/5020]; HELSCHER, THOMAS M [AG/1000]

Cc: LEADER, MICHAEL [AG/5020]; MCLEAN, KERYN [AG/5020]; TAYLOR, IAN N [AG/5020]; ARMSTRONG, JANICE M [AG/5340]; COMBEST, JOHN C [AG/1000]

Subject: RE: Roundup article in Fremantle Herald

Hi Honi

The reporter has printed the correct information that "Glyphosate is biodegradable but the surfactant is not". However, then she goes into a sensationalism mode quoting "studies" that suggest Roundup is not safe, which is probably derived from her interview of the Fremantle activist. I feel the response to FH needs to reiterate that her statement on biodegradability is correct, reiterate that Roundup is safe (and provide references), and if there are flaws in any of the studies quoted, point out these flaws.

Neil Anderson

QA & Formulations Lead, Asia Pacific

Monsanto Australia Ltd

Mobile phone: International 61409 382905; Australia 0409 382905

From: MCNAUGHTON, HONI JANINE [AG/5020]

Sent: Monday, September 21, 2009 10:56 AM

To: MCGREGOR, JOHN [AG/5020]; ANDERSON, NEIL J [AG/5020]; HELSCHER, THOMAS M [AG/1000]

Cc: LEADER, MICHAEL [AG/5020]; MCLEAN, KERYN [AG/5020]; TAYLOR, IAN N [AG/5020]; ARMSTRONG, JANICE M [AG/5340]; COMBEST, JOHN C [AG/1000]

Subject: Roundup article in Fremantle Herald

Importance: High

Hi John and Neil

The article in question has appeared in the Fremantle Herald as expected.

We need to think about our response. Possible suggestions:

- Letter from Scott's to the FH reiterating the correct information
- Letter from Monsanto to FH reiterating the safety of Roundup, etc

We may also need to compose a letter to all of Scott's Roundup customers (in WA) dismissing the allegations in the article. FH has a circulation of 20,000. However, the FTO concern is here in WA during this critical time.

· Keryn: You may want to contact DAFWA and other stakeholders as well as growers to explain what we plan to do.

· Ian: GSWG letter reiterating the safety of glyphosate from Steve Powles

Any actions and responses will need to be cleared with the US.

We will need to have a phone call about this including Scotts.

Please let me know your thoughts. I think you'll agree we need to jump on this.

Honi

Honi McNaughton  
Public Affairs Manager

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Monsanto's Blog: Monsanto According to Monsanto <<http://www.monsantoblog.com/>>

Monsanto For the Record: [http://www.monsanto.com/monsanto\\_today/for\\_the\\_record/default.asp](http://www.monsanto.com/monsanto_today/for_the_record/default.asp)  
<[http://www.monsanto.com/monsanto\\_today/for\\_the\\_record/default.asp](http://www.monsanto.com/monsanto_today/for_the_record/default.asp)>

1 observed adverse effects on health and the  
2 environment. Since it is an important  
3 objective to use environmentally safe and  
4 less toxic products, the polyoxyethylene  
5 tallowamine surfactants were replaced at  
6 least in some Monsanto products by others."

7 Was that true? Did you replace  
8 some of the Roundup products in Europe and  
9 stop using POA there?

10 A. I think you need to kind of go  
11 to the next sentence.

12 Q. Sure.

13 A. It fits in with what Mark said,  
14 the company, to say: My opinion was this  
15 formulation was fine, but the company then  
16 stated this decision was mainly based on eye  
17 irritation potential and the aquatic toxicity  
18 related to the formerly used substances.

19 We know that poly -- the POEA  
20 can be irritating to the eyes. It's  
21 reversible and not permanent. And because it  
22 is a surfactant, it can have toxicity to  
23 aquatic organisms.

24 Q. And to follow up on this from  
25 1999, just recently Europe has banned POEA in

1 the near future, right?

2 MR. JOHNSTON: Objection.

3 Vague.

4 Go ahead.

5 THE WITNESS: Based on a  
6 political decision, not on a  
7 toxicology position.

8 POEA is still used in the US  
9 and in Canada, completely approved and  
10 supported.

11 In my opinion and many other  
12 people's, that that was a political  
13 decision, not a safety decision.

14 QUESTIONS BY MR. MILLER:

15 Q. The answer is, yes, POEA will  
16 be off the market in Europe soon?

17 A. It will be off the market in  
18 Europe based on a political decision, not on  
19 a safety decision.

20 Q. Well, let's look at the  
21 decision to ban POEA in the European market.

22 (Farmer Exhibit 1-12 marked for  
23 identification.)

24 QUESTIONS BY MR. MILLER:

25 Q. We'll mark as Exhibit 1:12 a

1 European Commission fact sheet and ask if  
2 you've seen a copy of this. I have a copy  
3 for you and counsel.

4 You've seen this before,  
5 haven't you, ma'am?

6 A. I don't remember seeing this  
7 exact document, but I am aware of the  
8 discussions.

9 Q. Let's go then to page 2 of this  
10 document where it says, "What is the final  
11 decision?"

12 "The commission adopted the  
13 extension of the current approval for  
14 glyphosate in a limited period until the  
15 European Chemical Agency has concluded its  
16 review."

17 Do you see that?

18 A. Yes.

19 Q. Okay. "In parallel to the  
20 extension of the approval, the Commission has  
21 already presented Member States a series of  
22 recommendations on the use of glyphosate.  
23 Discussions with the Member States have  
24 started at an expert level, and the  
25 Commission will work to have them adopted as

1 soon as possible. The decision will contain  
2 three clear recommendations: Number 1, ban a  
3 co-formulant called POE-tallowamine from  
4 glyphosate-based products," right?

5 A. That's what it says there.

6 Q. And that's the POEA we've been  
7 talking about, right?

8 A. Yes, it is.

9 Q. And the other recommendation is  
10 "minimize the use of the substance in public  
11 parks, public playgrounds and gardens,"  
12 right?

13 A. That's what it says there, yes.

14 Q. "Minimize the pre-harvest use  
15 of glyphosate," right?

16 A. Yes, that's what it says there.

17 Q. Okay. And you're --

18 A. But, again -- I'm sorry.

19 Q. No, go ahead. I didn't mean to  
20 cut you off.

21 A. Again, I want to point out that  
22 nowhere in here it talks about the safety of  
23 POEA and that they are fully approved in US  
24 and Canada. And this is a political  
25 decision.

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UNITED STATES DISTRICT COURT  
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP )  
PRODUCTS LIABILITY ) MDL No. 2741  
LITIGATION )  
\_\_\_\_\_ ) Case No.  
THIS DOCUMENT RELATES ) 16-md-02741-VC  
TO ALL CASES )

THURSDAY, JANUARY 12, 2017  
CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER  
- - -

Videotaped deposition of Donna Farmer, Ph.D., Volume II, held at the offices of HUSCH BLACKWELL, L.L.C., 190 Carondelet Plaza, Suite 600, St. Louis, Missouri, commencing at 9:07 a.m., on the above date, before Carrie A. Campbell, Registered Diplomate Reporter, Certified Realtime Reporter, Illinois, California & Texas Certified Shorthand Reporter, Missouri & Kansas Certified Court Reporter.

- - -  
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1 ingredient in the formulated product.

2 And then as we talked about  
3 yesterday, there are other substances called  
4 inerts. The two major inerts that we find in  
5 glyphosate-based formulations are a  
6 surfactant, which is like a soapy-like  
7 substance, and then water, a lot of water.

8 Q. So glyphosate-marketed products  
9 contain glyphosate, water and some sort of  
10 surfactant usually?

11 A. The majority, yes.

12 Q. And we call those formulated  
13 products?

14 A. Formulated products.

15 Q. Okay. And you reference the  
16 term "inert ingredients."

17 Can you tell me what that  
18 means?

19 A. Inert ingredients are other  
20 ingredients put in a pesticide formulation.  
21 It doesn't mean that they are inert. They  
22 have biological activity, but they don't  
23 provide a pesticidal activity.

24 So those -- you have your  
25 active ingredient and your inert ingredients



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES,  
AND TOXIC SUBSTANCES

**MEMORANDUM**

**Date:** 3-JUN-2009

**SUBJECT:** **Glyphosate.** Human-Health Assessment Scoping Document in Support of Registration Review.

**PC Codes:** 103601; 103603; 103604;  
103605; 103607; 103608; 103613;  
417300

**DP Barcode:** D362745

**Decision No.:** 407032

**Registration No.:** N/A

**Petition No.:** N/A

**Regulatory Action:** Registration Review Scoping Document

**Risk Assessment Type:** N/A

**Case No.:** N/A

**TXR No.:** N/A

**CAS Nos.:** 38641-94-0, 70393-85-0, 40465-66-5,  
?, 69254-40-6, 34494-04-7, 70901-20-1, 1071-83-6

**MRID No.:** N/A

**40 CFR:** §180.364

**FROM:** Julie M. Langsdale, MPH, Environmental Health Scientist  
Tom Bloem, Chemist  
Kelly M. Lowe, Environmental Scientist  
Robert Mitkus, Ph.D., Toxicologist  
Risk Assessment Branch 1 (RAB1)  
Health Effects Division (HED, 7509P)  
Office of Pesticide Programs (OPP)

**THROUGH:** Dana M. Vogel, Branch Chief  
George F. Kramer, Ph.D., Senior Chemist  
RAB1/HED/OPP (7509P)

**TO:** John Pates/Susan Lewis  
Special Review and Reregistration Division (SRRD)/OPP (7508P)

Attached is HED's human-health risk assessment scoping document for glyphosate to support Registration Review.

## Executive Summary

Glyphosate is a non-selective herbicide which acts via blocking the activity of the enzyme, 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS). EPSPS is produced only by green plants and is involved in the synthesis of the amino acids tyrosine, tryptophan, and phenylalanine. Glyphosate is registered for use on a variety of fruit, vegetable, and field crops as well as for aquatic and terrestrial uses. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. The most recent human-health risk assessment for glyphosate was completed in 2006 (Memo, J. Tomerlin, 29-Sep-06, D321992). Since that risk assessment, HED has reviewed petitions for application of glyphosate to certain transgenic crops and concluded that revisions to the 29-Sep-2006 risk assessment were unnecessary at the time of review.

Glyphosate is of low acute toxicity following oral, dermal, and inhalation exposure. An acute dose and endpoint have not been selected for any population subgroups because no effects that could be attributed to a single exposure (dose) were observed in oral toxicity studies including the developmental toxicity studies in rats and rabbits. Glyphosate has been classified as a "Group E" chemical (evidence of non-carcinogenicity for humans), based upon lack of convincing evidence of carcinogenicity in adequate studies in two animal species (mice and rats). No significant reproductive or developmental toxic effects were found in toxicity studies in the rat and rabbit. Neurotoxicity has not been observed in any of the acute, subchronic, chronic, developmental, or reproductive studies performed with glyphosate. However, new data requirements which include the requirement of an acute neurotoxicity study and a subchronic neurotoxicity study, as well as an immunotoxicity study, have been established under 40 CFR Part 158 for registration of pesticides for food and non-food uses.

Aminomethylphosphonic acid (AMPA) is a metabolite of glyphosate. In 1992, the HED Metabolism Committee determined that, based on toxicological considerations, AMPA need not be regulated, and in 1994, it was determined that, based on toxicological considerations, AMPA need not be regulated regardless of levels observed in foods or feeds. *N*-acetyl-glyphosate is a metabolite of glyphosate which is formed in certain transgenic crops and is considered to be equally toxic as glyphosate (Memo, T. Bloem, 18-Mar-08, D345923). *N*-acetyl-AMPA was detected as one of the metabolites formed in these crops and was excluded as a residue of concern based on residue and toxicity considerations (Memo, T. Bloem, 18-Mar-08, D345923). The decision that AMPA and *N*-acetyl-AMPA need not be regulated, regardless of levels observed in foods or feeds, may be revisited during the registration review process.

The dietary-exposure database is adequate to support the existing registrations. An acute dietary-exposure assessment was not required because no acute toxicological endpoint has been determined for glyphosate. The 2006 chronic dietary-exposure assessment for glyphosate was conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM<sup>TM</sup>-FCID, ver. 2.03), and incorporated tolerance-level residues, 100% crop treated data for all commodities, and worst-case scenario drinking water exposure estimates. The residue chemistry database is sufficient to support the current registrations; however, there are some outstanding studies for some of these registrations which, if submitted, would change the registration status from conditional to unconditional.

A new residential exposure risk assessment is required due to the registration of a new residential-use product with an application rate which is higher than the rate previously assessed. A new aggregate risk assessment will need to be conducted once the residential exposure risk assessment has been completed. The increase in the residential application rate is not expected to lead to residential exposures which exceed HED's level of concern (margins of exposure (MOEs)<100) or affect the aggregate risk in such a way that it exceeds HED's level of concern. No occupational handler or occupational post-application assessments were required because no short-term dermal or inhalation toxicity endpoints were identified by HED.

The U.S., Mexico, and Codex residue definitions are harmonized. There are discrepancies between the Canadian residue definition and residue definitions of the U.S., Mexico, and Codex. For some raw agricultural and livestock commodities, the tolerance and Maximum Residue Limits (MRLs) for the U.S., Canada, Mexico, and Codex are harmonized; however there are a variety of tolerances and MRLs for commodities which are not harmonized.

## **Introduction**

HED has evaluated the status of the human-health assessments for glyphosate to determine if sufficient data are available and if any updates are required to support Registration Review. HED has considered the most recent human-health risk assessment for glyphosate (Memo, J. Tomerlin, 29-Sep-06, D321992); the most recent human-health risk assessment for glyphosate applied to transgenic crops (Memo, T. Bloem, 18-Mar-08, D345923); updates to its toxicity, exposure, and usage databases; and the most updated Agency science policy and risk assessment methodologies to determine the scope of work necessary to support Registration Review. In addition, HED conducted an open search to look for new literature relevant to the human-health risk assessment.

Glyphosate is a non-selective herbicide registered for use on a variety of fruit, vegetable, and field crops. Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way. Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A.

The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed.

Since the glyphosate RED (Reregistration Eligibility Decision) was completed in 1993, the following commodities have been assessed and registered: Aloe vera; Ambarella; Artichoke, globe; Bamboo, shoots; Betelnut; Biriba; Blimbe; Borage, seed; Cacao bean; Cactus, fruit; Cactus, pads; Canola, meal; Canola, seed; Cattle, kidney; Cattle, liver; Chaya; Crambe, seed; Custard apple; Dokudami; Durian; Egg; Epazote; Feijoa; Flax, meal; Flax, seed; Galangal, roots; Ginger, white, flower; Gourd, buffalo, seed; Governor's plum; Gow kee, leaves; Herbs subgroup 19A; Hop, dried cones; Ilama; Imbe; Imbu; Kava roots; Kenaf, forage; Lesquerella, seed; Leucaena, forage; Mangosteen; Meadowfoam, seed; Mioga, flower; Mustard, seed; Noni; Nut, pine; Okra; Oregano, Mexican, leaves; Palm heart; Palm heart, leaves; Papaya, mountain; Pawpaw; Pepper leaf, fresh leaves; Perilla, tops; Pulasan; Quinoa, grain; Rambutan; Rose apple; Safflower; Salal; Sapote, mamey; Sesame, seed; Spanish lime; Spice subgroup 19B; Star apple; Starfruit; Stevia, dried leaves; Strawberry; Surinam cherry; Teff, grain; Ti, leaves; Ti, roots; Ugli fruit; Wasabi, roots; Water spinach, tops; Watercress, upland; Wax jambu; and Yacon, tuber.

The qualitative nature of glyphosate residues in plants and livestock is adequately understood. The terminal residue to be regulated in nontransgenic plants and transgenic corn and canola modified to express the *Agrobacterium sp.* EPSPS and oxireductase genes is glyphosate *per se*. For crops (currently soybeans and corn) which have a transgenic variety that has been engineered to express the microbial glyphosate acetyltransferase gene (*gat4601*), the combined residues to be regulated are glyphosate and *N*-acetyl-glyphosate. The residue chemistry database is sufficient to support the current registrations; however, there are some outstanding studies which, if submitted, would change the registration status from conditional to unconditional.

Data needs and risk assessment updates required under registration review for glyphosate are as follows:

- An immunotoxicity study, acute neurotoxicity study, and a subchronic neurotoxicity are required as specified in the new 40 CFR Part 158 data requirements.
- Two toxicology studies (MRIDs 47311001 and 47311004) have been submitted which are still in the process of being reviewed. Once the reviews are complete, the reviews need to be added to the Integrated Hazard Assessment Database (IHAD).
- Nature of the residue studies in plants and livestock and ruminant and poultry feeding studies which were requested in recent HED Memos (Memo, T. Bloem, 18-Mar-08, D345923; and Memo, T. Bloem, 29-Oct-08, D357880) are still required.
- A new residential exposure risk assessment is required due to the registration of a new residential-use product with an application rate which is higher than the rate previously assessed.
- A new aggregate risk assessment is required once the residential exposure risk assessment has been completed.

## Hazard Identification/Toxicology

### *Glyphosate*

Glyphosate is a non-selective herbicide which acts via blocking the activity of EPSPS. EPSPS is produced only by green plants and is involved in the synthesis of the amino acids tyrosine, tryptophan, and phenylalanine.

Glyphosate is of low acute toxicity following oral, dermal, and inhalation exposure, since all studies are in Toxicity Category III or IV. It is a mild eye irritant (Toxicity Category III), slight skin irritant (Toxicity Category IV), and is not a dermal sensitizer in guinea pigs. Inhalation risk assessments (any time period) are not required based on the low toxicity of the formulation products (Toxicity Category III or IV) and the physical characteristics of the technical product (wet cake). An acute dose and endpoint have not been selected for any population subgroups because no effects that could be attributed to a single exposure (dose) were observed in oral toxicity studies including the developmental toxicity studies in rats and rabbits. Therefore, a dose and endpoint were not identified for acute dietary risk assessment.

A chronic feeding/carcinogenicity study in rats found no systemic effects in any of the parameters examined (body weight, food consumption, clinical signs, mortality, clinical pathology, organ weights, and histopathology). In a second chronic feeding/carcinogenicity study in rats tested at higher dietary levels, a lowest-observed-adverse-effect level (LOAEL) was identified at 20,000 parts per million (ppm; approximately 940 mg/kg/day) based on decreased body weight gains in the females and increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight, and increased relative liver weight/brain weight in males. No evidence of carcinogenicity was found in rats. There was also no evidence of carcinogenicity in mice. In a chronic toxicity study in dogs, no systemic effects were found in all examined parameters.

On 26-Jun-1991, the HED Carcinogenicity Peer Review Committee (CPRC) evaluated the weight of the evidence on glyphosate with particular emphasis on its carcinogenic potential. The Committee concluded that glyphosate should be classified as a "Group E" chemical (evidence of non-carcinogenicity for humans), based upon lack of convincing carcinogenicity evidence in adequate studies in two animal species (mice and rats).

Acceptable developmental toxicity studies in the rat and rabbit are available, as is an acceptable 2-generation reproduction study in the rat. No significant reproductive and developmental toxic effects were found. A focal tubular dilation of the kidneys was observed in a three-generation reproductive study on rats at the 30-mg/kg/day level [highest dose tested (HDT)], however a two-generational reproductive study on rats did not observe the same effect at the 1500-mg/kg/day level (HDT), nor were any adverse reproductive effects observed at any dose level. In 1991, the HED Reference Dose (RfD) Committee concluded that the focal tubular dilation of the kidneys at the 30-mg/kg/day level was a spurious rather than a glyphosate-related effect.

In a prenatal developmental toxicity study in rats, maternal (systemic) effects observed included mortality, increased clinical signs, and reduced body-weight gain at the HDT (3500 mg/kg/day). Developmental (fetal) effects were observed only in the high-dose group and included decreases

in total implantations/dam and nonviable fetuses/dam, increased number of litters and fetuses with unossified sternebrae, and decreased mean fetal body weights. In a prenatal developmental toxicity study in rabbits, maternal (systemic) effects observed included mortality and clinical signs of toxicity at the HDT (350 mg/kg/day). In the rabbits, developmental toxicity was not observed at any dose. On the basis of developmental studies in rats and rabbits and reproductive findings in rats, glyphosate exhibited no evidence of increased susceptibility of offspring.

Neurotoxicity has not been observed in any of the acute, subchronic, chronic, developmental, or reproductive studies performed with glyphosate. New data requirements have been established under the revised 40 CFR Part 158 for registration of pesticides for food and non-food uses which include the requirement of an acute neurotoxicity study and a subchronic neurotoxicity study (Attachment 5). Similarly, 40 CFR Part 158 also requires an immunotoxicity study (Attachment 6).

The endpoints used for risk assessment purposes from the most recent human-health risk assessment (Memo, J. Tomerlin, 29-Sep-2006, D321992) can be found in Attachment 2.

The Food Quality Protection Act (FQPA) Safety Factor Committee (SFC) met on April 6, 1998 and addressed the potential enhanced sensitivity to infants and children as required by the FQPA (Memo, B. Tarplee, 17-Apr-98, TXR012584). The Committee recommended the 10x FQPA SF be reduced to 1x in assessing the risk posed by this chemical because: 1) there is no evidence of quantitative or qualitative increased susceptibility of the young demonstrated in the prenatal developmental studies in rats and rabbits and pre/post natal reproduction study in rats; 2) the toxicology database is adequate for FQPA assessment; 3) a developmental neurotoxicity study is not required and there was no evidence of neurotoxicity in any submitted study; and 4) the dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children.

#### *AMPA*

AMPA is a metabolite of glyphosate. In a 90-day oral toxicity study in rats, a LOAEL was identified for AMPA at 1200 mg/kg/day based on body weight loss and histopathological lesions of the urinary bladder. Previously the HED Metabolism Committee determined that, based on toxicological considerations, AMPA need not be regulated and should be dropped from the tolerance expression (Memo, R.B. Perfetti, 19-Aug-92). Furthermore, in a 17-Mar-94 meeting, the HED Metabolism Committee discussed whether uses that result in significantly higher residues of AMPA in plants and livestock commodities in the future would require that AMPA be reintroduced into the tolerance expression of glyphosate. The Committee determined that, based on toxicological considerations, AMPA need not be regulated regardless of levels observed in foods or feeds (Memo, R.B. Perfetti, 17-Mar-94).

#### *N-Acetyl-Glyphosate*

*N*-acetyl-glyphosate is a metabolite of glyphosate which is formed in certain transgenic crops. The acute oral LD<sub>50</sub> was greater than 5000 mg/kg in rats. Based on structural similarity with glyphosate, structure-activity relationships [(SAR); lack of structural alerts for carcinogenicity, mutagenicity, and endocrine effects], low acute toxicity, low subchronic toxicity, and lack of mutagenicity, *N*-acetyl-glyphosate is considered to be equally toxic as glyphosate.

### *N-Acetyl-AMPA*

*N*-acetyl-AMPA is a minor metabolite of glyphosate which is formed in certain transgenic crops. *N*-acetyl-AMPA is expected to be of low acute toxicity and was negative for mutagenicity. It is not expected to be absorbed quickly from the gastrointestinal (GI) tract since it is a charged molecule at the physiological pH. Therefore, it is expected to be less toxic than *N*-acetyl-glyphosate. The metabolism study in rats with *N*-acetyl-glyphosate indicated that about 99% of the parent compound was isolated in the excreta. Based on this and the minimal plant residue concentrations, *N*-acetyl-AMPA was excluded as a residue of concern.

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) “may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC’s recommendation that the Program include evaluations of potential effects in wildlife. When the appropriate screening and/or testing protocols being considered under the Agency’s Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, glyphosate may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

### **Conclusions**

As specified in the new 40 CFR Part 158 data requirements, immunotoxicity, acute neurotoxicity, and subchronic neurotoxicity studies should be conducted. The decision that AMPA need not be regulated, regardless of levels observed in foods or feeds, may be revisited during the registration review process.

### **Residue Chemistry**

The qualitative nature of glyphosate residues in plants and livestock is adequately understood. Metabolism studies conducted with nontransgenic corn, cotton, soybeans, and wheat were previously submitted and reviewed. Based on these data, HED concluded that the residue of concern in/on nontransgenic plants is glyphosate *per se* (Memo, R. Perfetti, 19-Aug-1992; Memo, R. Perfetti, 27-Oct-1992, D183202; Memo, R. Perfetti, 17-Mar-1994). Metabolism studies have also been submitted on glyphosate-tolerant canola (Memo, T. Bloem, 30-Nov-1998, D242628) and glyphosate-tolerant corn (Memo, G. Kramer, 14-Mar-1996, D217539). The glyphosate-tolerant canola and corn were genetically modified to express the EPSPS gene derived from *Agrobacterium sp.* (strain CP4) which codes for an EPSPS protein that has reduced affinity for glyphosate as compared to the endogenous EPSPS protein. The glyphosate-tolerant canola and corn were also genetically engineered to express the oxireductase gene which converts glyphosate to the nonherbicidal AMPA. Metabolism in these varieties of transgenic canola and corn was essentially the same as the nontransgenic plants. Therefore, it was concluded that the terminal residue to be regulated in nontransgenic plants and transgenic corn

and canola modified to express the *Agrobacterium sp.* EPSPS and oxireductase genes is glyphosate *per se*.

Subsequent to this decision, DuPont submitted and HED approved a request permitting the commercialization of a new transgenic variety of soybean [Optimum™ GAT™ soybean (DP-356043-5)]. The Optimum™ GAT™ soybean was engineered to express the microbial glyphosate acetyltransferase gene (*gat4601*), which confers tolerance to glyphosate via acetylation of the secondary amine group of glyphosate (results in formation of the nonherbicidal *N*-acetyl-glyphosate). As a result of the introduction of this seed line, HED concluded that the residues of concern in/on plants for tolerance expression and risk assessment should change from glyphosate *per se* to the combined residues of glyphosate and *N*-acetyl-glyphosate (T. Bloem, 12-Mar-2008, D346713). Following this decision, it was determined that only the tolerance expression for soybeans would change from glyphosate *per se* to the combined residues of glyphosate and *N*-acetyl-glyphosate; the tolerance expression for all other crops would remain as glyphosate *per se*. Studies were then submitted by DuPont and reviewed by HED for Optimum™ GAT™ field corn, a transgenic variety of corn which expresses the microbial glyphosate acetyltransferase gene (*gat4601*). This submission resulted in a change to the tolerance expression for field corn from glyphosate *per se* to the combined residues of glyphosate and *N*-acetyl-glyphosate (Memo, T. Bloem, 29-Oct-08, D357880).

The residue chemistry database is sufficient to support the current registrations; however, there are some outstanding studies regarding the recent Optimum™ GAT™ soybeans and Optimum™ GAT™ field corn submissions which, if submitted, would change the registration status from conditional to unconditional (Memo, T. Bloem, 18-Mar-08, D345923; and Memo, T. Bloem, 29-Oct-08, D357880). The requested studies include nature of the residue studies in plants and livestock, and ruminant and poultry feeding studies. See the data requirements section for more information.

### **Conclusions**

The qualitative nature of glyphosate residues in plants and livestock is adequately understood. The terminal residue to be regulated in nontransgenic plants and transgenic corn and canola modified to express the *Agrobacterium sp.* EPSPS and oxireductase genes is glyphosate *per se*. For crops (currently soybeans and corn) which have a transgenic variety that has been engineered to express the microbial glyphosate acetyltransferase gene (*gat4601*), the combined residues to be regulated are glyphosate and *N*-acetyl-glyphosate. The residue chemistry database is sufficient to support the current registrations; however, there are some outstanding studies which, if submitted, would change the registration status from conditional to unconditional.

### **Dietary Exposure**

The most recent chronic dietary-exposure assessment was performed in conjunction with the September 2006 human-health risk assessment. No toxicological endpoint attributable to a single dose of glyphosate was identified by HED; therefore, an acute dietary-exposure assessment was not conducted. Glyphosate is classified as not likely to be a human carcinogen, so a cancer dietary-exposure analysis is not required. Chronic dietary risk assessments were conducted using DEEM™-FCID, ver. 2.03. DEEM™-FCID incorporates the food consumption

data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII; 1994-1996 and 1998).

The chronic analyses incorporated tolerance-level residues, 100% crop treated data for all commodities, and drinking water exposure estimates. The analysis used drinking water estimates from the direct application of glyphosate to water (230 ppb), which is the most conservative drinking water estimate. EFED has confirmed that the concentration estimate from the direct application of glyphosate to water is still the worst-case scenario estimate for the possible concentration of glyphosate in water.

Based on the 2006 analysis, the chronic exposure estimate of the U.S. population is 2% of the chronic population-adjusted dose (cPAD) and is, therefore, less than HED's level of concern (<100% of the cPAD). Infants <1 year old represent the most highly exposed population subgroup at 7% of the cPAD.

### ***Conclusions***

The dietary-exposure database is adequate to support the existing registrations. HED does not require a new chronic dietary risk assessment at this time because the most recent assessment incorporated concentration estimates from the direct application of glyphosate to water, and these estimates still represent the worst-case scenario. If any decisions regarding residues requiring regulation are made during the registration review process, a new dietary-exposure analysis may be required.

### **Residential Exposure**

Glyphosate, a non-selective herbicide, is registered for broadcast and spot treatments on home lawns and gardens. Glyphosate products for homeowner use are packaged as ready-to-mix formulations and ready-to-use sprayers and are common in home and garden stores in the U.S. Glyphosate products are used by lawn care operators (LCOs) for broadcast and spot treatment weed control programs on homeowner lawns. Glyphosate products are also labeled for turf renovation.

Glyphosate is registered for use in recreational areas, including parks and golf courses for control of broadleaf weeds and grasses. Additional registered uses include applications to lakes and ponds, including reservoirs, for non-selective control of nuisance aquatic weeds.

#### ***Residential Handlers***

Based on the registered residential use patterns, there is a potential for short-term dermal and inhalation exposures to homeowners who mix and apply products containing glyphosate (residential handlers). However, since short- and intermediate-term dermal or inhalation endpoints were not selected, no residential handler assessment is needed.

#### ***Residential Post Application***

Post-application dermal and inhalation assessments are not needed since short- and intermediate-term dermal or inhalation endpoints were not selected. However, based on the registered use patterns, toddlers may have short-term post-application incidental oral exposures from hand-to-

mouth behavior on treated lawns and swimmers may to have short-term post-application incidental oral exposures from aquatic uses.

The Agency previously assessed post-application incidental oral ingestion exposure for toddlers in the most recent HED human-health risk assessment (Memo, J. Tomerlin, 29-Sep-2006, D321992). The standard operating procedures (SOPs) for Residential Exposure Assessments, Draft, 17-Dec-1997 and Exposure Science Advisory Committee (ExpoSAC) Policy No. 11, 22-Feb-2001: Recommended Revisions to the SOPs for Residential Exposure were used to estimate post-application incidental oral ingestion exposures and risk estimates for toddlers.

Also assessed were incidental oral exposures for adult, children, and toddler swimmers may have short-term post-application incidental ingestion exposures. The exposure assumptions used in the swimmer assessment are based on HED's Standard Operating Procedures for Residential Exposure Assessments, Draft, 17-Dec-1997 and subsequent updates for swimming pools adapted for this assessment, but the Residential SOP assumptions are considered conservative for use in assessing this scenario.

While adult and child golfers may have short-term post-application dermal exposure at golf courses, no dermal assessments were required because HED did not identify short- or intermediate-term dermal endpoints.

In the 2006 risk assessment, the MOEs for post-application toddler oral exposures were calculated using the highest application rate (1.62 lb ae/A) registered at the time of assessment. All of these MOEs were greater than 100 and did not exceed HED's level of concern for residential exposures (MOEs <100). In October of 2008, a new residential use product (Roundup<sup>®</sup> Weed & Grass Killer Super Concentrate; EPA Reg. No. 71995-25) was registered which has a higher application rate (10.5 lb ae/A). This new application rate is not expected to lead to residential exposures which exceed HED's level of concern (MOEs <100); however, a new residential exposure risk assessment is required.

MOEs for post-application exposure of swimmers to glyphosate after aquatic weed control applications are greater than 100 and do not exceed HED's level of concern for short-term non-occupational (recreational) exposures (MOEs <100). See Attachment 3 for a table which summarizes residential post-application use patterns and corresponding MOEs. Based on the new residential use product (EPA Reg. No. 71995-25) which has a higher rate of application (10.5 lb ae/A), the residential exposures and MOEs for toddlers presented in Attachment 3 will change; however the increased application rate is not expected to lead to exposures which exceed HED's level of concern for residential exposures (MOEs <100). These changes will be reflected in the new residential exposure risk assessment.

### ***Conclusions***

There is sufficient information available to assess residential exposure. A new residential exposure risk assessment is required due to the registration of a new residential-use product with an application rate which is higher than the rate previously assessed. The new application rate is not expected to lead to residential exposures which exceed HED's level of concern (MOEs <100).

## **Aggregate Risk Assessment**

In the most recent HED human-health risk assessment (Memo, J. Tomerlin, 29-Sep-06, D321992), aggregate risk assessments were performed for short-, intermediate-term and chronic exposures. No toxicological endpoint attributable to a single dose of glyphosate has been identified by HED, so an acute aggregate risk analysis was not conducted. A cancer risk assessment was not conducted because there has been no evidence of carcinogenicity in any glyphosate toxicity study, and glyphosate has been classified as negative for carcinogenicity in humans.

In aggregating short- and intermediate-term risk, the Agency considered background chronic dietary exposure (food + water) and short- and intermediate-term incidental oral exposures. The Agency conducted the risk assessment using residential turf exposures estimates because the incidental oral ingestion exposure estimates for toddlers from residential turf exposures exceeded the estimates from post-application swimmer exposures and represented the worst-case scenario. Exposures from the swimmer and residential turf scenarios were not combined due to the low probability of both occurring.

In the 2006 risk assessment, dietary (food + water) exposures were combined with the estimated residential exposure and the combined exposure was then used to calculate an MOE for aggregate risk. The total short- and intermediate-term food and residential aggregate MOEs for children 1-2 years of age and adults 20-49 years old were 1400 and 4610, respectively. Since these MOEs are greater than 100, the short- and intermediate-term aggregate risk does not exceed HED's level of concern. The short- and intermediate-term aggregate risk section of the 2006 risk assessment identified children 1-2 years old as the most highly exposed population subgroup; however, the chronic dietary analysis identified all infants <1 year old as the most highly exposed population subgroup. This is not expected to change the MOE in such a way that it will exceed HED's level of concern.

Because no residential uses result in long-term exposure, the long-term aggregate risk did not include estimates of residential risk. Since water residues were incorporated into the chronic dietary risk assessment, the chronic dietary risk assessment also provides the estimate of long-term aggregate risk. The long-term aggregate risk does not exceed HED's level of concern.

A new aggregate risk assessment, which takes into account the new estimated residential exposures, will need to be conducted once the updated residential exposure risk assessment has been completed. The increase in the residential application rate, and subsequent change in estimated residential exposures, is not expected to affect the aggregate risk in such a way that it exceeds the Agency's level of concern.

## **Conclusions**

The 2006 aggregate risk assessment found no risks of concern; however due to the registration of a product with a higher application rate than previously assessed, a new aggregate risk assessment will need to be conducted once the residential exposure risk assessment has been completed. The increase in the residential application rate, and subsequent change in estimated residential exposures, is not expected to affect the aggregate risk in such a way that it exceeds

HED's level of concern. If decisions regarding residues requiring regulation or new toxicological considerations are made during the registration review process, these decisions will be taken into account in the new aggregate exposure assessment.

### **Occupational Exposure**

Glyphosate is a non-selective herbicide registered for use on a variety of fruit, vegetable, and field crops. Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way. Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment.

#### *Occupational Handlers*

Based on the registered uses of glyphosate, commercial handlers and grower/applicators are expected to have short-term dermal and inhalation exposures. No handler assessment was required because no short-term dermal or inhalation endpoints were selected.

#### *Occupational Post Application*

Occupational post-application assessments are not required because no short-term dermal or inhalation endpoints were selected by HED. Exposures from occupational and/or residential uses of glyphosate are not expected to pose undue risks.

### **Conclusions**

Since no short-term dermal or inhalation endpoints were identified, no occupational handler or occupational post-application assessments were required.

### **Public Health and Pesticide Epidemiology Data**

A summary report listing incidents for glyphosate reported to the OPP Incident Data System (IDS) has been provided for the docket (Memo, M. Hawkins, 12-Mar-09). The report represents incidents occurring in the U.S. from 2002 to the present for glyphosate only. Since 2002, 289 incidents regarding glyphosate have been reported.

#### *Human Incident Data: OPP IDS (2009)*

The OPP IDS was consulted for poisoning incident data on the active ingredient glyphosate. The purpose of the database search was to identify potential patterns in the extent and severity of the health effects attributed to glyphosate exposure. The IDS includes reports of incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6 (a) (2) reports from registrants, other federal, state health, and environmental agencies, and individual consumers. The following databases were not searched for poisoning incident data: the American Association of Poison Control Centers Toxic Exposure Surveillance

System (TESS), the California Pesticide Illness Surveillance Program, and the National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR).

Reports of adverse health effects allegedly due to a specific pesticide exposure (an "incident") are largely self-reported and therefore, neither exposure to a pesticide nor reported symptom (or the connection between the two) is validated. However, incident information can be an important feedback loop to the Agency; incidents of severe outcome, or a suggested pattern or trend among less severe incidents can signal the Agency to further investigate a particular chemical or product.

FIFRA Section 6(a)(2) includes reports of alleged human health incidents from various sources, including mandatory reports from registrants, other federal, state health, and environmental agencies, and individual consumers. Since 1992, OPP has compiled these reports in an IDS. The majority of reports submitted to the IDS represent anecdotal reports or allegations only. Typically, OPP does not draw firm conclusions implicating the pesticide is causally associated with the reported health effects. Nevertheless, in some instances if enough cases and/or documentation of exposure and health effect or suggested patterns of exposure and response are indicative of a strong relationship, risk mitigation measures may be suggested.

The incident report identified that 289 case reports, which were allegedly attributable to glyphosate, were reported to the IDS between 2002 and 2008. The written content of each summarized case-report was reviewed to determine the health effects most commonly reported to be associated with glyphosate use/exposure. Eight major types of adverse health effects were identified through IDS: gastro-intestinal (4.8%), dermal (30.1%), upper-respiratory (10.3%), neurological (34.3%), cardiovascular (0.3%), ocular (13.8%), muscular (0.3%), and combination (5.5%) effects. Only 2 case reports (0.7%) alleged exposure with no symptoms reported. Disturbances of the gastrointestinal and neurological systems are congruent with classic organophosphate exposure within the GI system. Among the case reports, gastrointestinal effects reported included diarrhea, abdominal cramps, and stomach pain. Neurological system effects included shaking, loss of coordination, tingling, neuropathy, ataxia, and numbness. Dermal effects included blisters, rash, pruritus, skin irritation, hives, welts, sores, burning skin, and peeling skin. Many of the dermal cases were associated with splashing and/or leaking of the product onto the hands. Among the case reports, the majority of the reported symptoms involved dermal and neurological effects.

Glyphosate exhibits low toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV). Glyphosate is a mild eye irritant, a slight dermal irritant, and is not a dermal sensitizer.

**Table 1. Major Types of Health Effects Identified through the IDS Search.**

Symptoms	Frequency (%)
Dermal	87 (30.1)
Gastro-intestinal	13 (4.8)
Upper Respiratory	30 (10.3)
Neurological	99 (34.3)

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<b>Table 1. Major Types of Health Effects Identified through the IDS Search.</b>	
<b>Symptoms</b>	<b>Frequency (%)</b>
Combination	16 (5.5)
Ocular	40 (13.8)
Muscular	1 (0.3)
Cardiovascular	1 (0.3)
No Symptoms	2 (0.7)
<b>Total</b>	<b>100<sup>1</sup></b>

<sup>1</sup>Overall frequency does not total 100% due to rounding.

### *Agricultural Health Study*

The Agricultural Health Study (AHS) is a prospective cohort study of licensed private and commercial pesticide applicators and their spouses recruited in Iowa and North Carolina. A total of 89,658 people are enrolled, and 57,311 of these participants are private or commercial pesticide applicators. Potential causes of cancer and other diseases among farmers, their families, and commercial pesticide applicators are explored through the study. The AHS began recruitment in 1993 and is currently in Phase III of the study. Additional information about the AHS can be found on the study website: <http://aghealth.nci.nih.gov/index.html>.

A number of publications regarding pesticide exposure have resulted from the AHS. In a study (De Roos *et al.*, 2005) which looked at the cancer incidence among glyphosate-exposed commercial and private pesticide applicators in the AHS, De Roos *et al.* evaluated the associations between glyphosate exposure and incidence of all cancers combined and 12 relatively common cancer subtypes. Among the enrolled AHS pesticide applicators, 41,035 (75.5%) reported having ever used glyphosate and more than 97% of those participants who had used glyphosate were men. De Roos *et al.* identified glyphosate exposure as: “a) ever personally mixed or applied products containing glyphosate; b) cumulative lifetime days of use, or ‘cumulative exposure days’ (years of use x days/year); and c) intensity-weighted cumulative exposure days (years of use x days/year x estimated intensity level)” (De Roos *et al.*, 2005). For the purpose of this study, the time period used to identify incident cancers was from the date of enrollment through 31-Dec-2001. To estimate the exposure-response relationship between glyphosate and incidence of cancer, Poisson regression analyses were used. No association was found between glyphosate exposure and all cancer incidence or most of the specific cancer subtypes which were evaluated by the study. However, the study did find, based on a small number of cases, a suggested association between multiple myeloma and glyphosate exposure. The researchers recommended for additional follow up on the suggested association as more multiple myeloma cases occur within the AHS cohort.

### *Conclusions*

A summary report listing incidents for glyphosate reported to the OPP IDS has been provided for the docket (Memo, M. Hawkins, 12-Mar-09; no DP barcode). The report represents incidents occurring in the U.S. from 2002 to the present for glyphosate only. Since 2002, 289 incidents regarding glyphosate have been reported. Eight major types of adverse health effects were identified through IDS including gastro-intestinal, dermal, upper-respiratory, neurological, cardiovascular, ocular, muscular, and combination effects. The IDS query resulted in a moderately large number of case reports which warrants searching the following databases for

consistency and reproducibility of the poisoning incident data: TESS, the California Pesticide Illness Surveillance Program, and NIOSH SENSOR. The reported incidents from the TESS, California Pesticide Illness Surveillance Program, and NIOSH SENSOR databases will be screened in more detail during the development of the Final Work Plan for glyphosate.

A study using AHS data which looked at the cancer incidence among glyphosate-exposed pesticide applicators did not find an association between glyphosate exposure and cancer incidence overall or with most cancer subtypes. A suggested association between multiple myeloma and glyphosate exposure was identified; however, the number of multiple myeloma cases in the AHS cohort was small. As more cases occur, this association should be revisited.

### **Tolerance Assessment and International Harmonization**

U.S. permanent tolerances (listed in 40 CFR 180.364) and MRLs are summarized in Table 6 (Attachment 4). The U.S., Mexico, and Codex residue definitions are harmonized. There are discrepancies between the Canadian residue definition and residue definitions of the U.S., Mexico, and Codex. Canada, Mexico, and Codex have established MRLs for residues of glyphosate in/on several raw agricultural and livestock commodities, but several MRLs are not harmonized with U.S. tolerances. Specific limits which do not appear to be harmonized include: animal feed, nongrass, group 18; banana; canola, seed; cattle, meat byproducts; corn, field, grain; cotton, undelinted seed; flax, seed; fruit, citrus, group 10; goat, meat byproducts; grain, cereal, forage, fodder and straw, group 16, except field corn, forage; grain, cereal, group 15 except field corn, popcorn, rice, sweet corn, and wild rice; grass, forage, fodder and hay, group 17; hog, meat byproducts; mustard, seed; pea, dry; poultry, meat; poultry, meat byproducts; sheep, meat byproducts; soybean, seed; sugarcane, molasses; sunflower, seed; and vegetable, legume, group 6 except soybean and dry pea. These discrepancies have been bolded in Table 6.

#### *Additional Information on Status from other Regulatory Agencies*

- The European Union reviewed glyphosate in 2002 and it was included in Annex 1.
- Glyphosate has been given a "low" priority for assessment in California, which means that there has been no activity on it so far, and it is not being considered among those of most concern for risk assessment. If an issue of concern arises, the priority status of glyphosate could change.
- The Pest Management Regulatory Agency (PMRA) is in the process of developing a schedule for the review of glyphosate.

### **Conclusions**

The U.S., Mexico, and Codex residue definitions are harmonized. There are discrepancies between the Canadian residue definition and residue definitions of the U.S., Mexico, and Codex. For some raw agricultural and livestock commodities, the tolerances and MRLs for the U.S., Canada, Mexico, and Codex are harmonized; however there are a variety of commodities for which the tolerance and MRLs are not harmonized.

## **Environmental Justice**

Potential areas of environmental justice concerns, to the extent possible, were considered in the human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf>). The OPP typically considers the highest potential exposures from the legal use of a pesticide when conducting human-health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

## **Cumulative**

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to glyphosate and any other substances, and glyphosate does not appear to produce a toxic metabolite produced by other substances. Prior to a final Registration Review decision for glyphosate, the Agency will determine if there is any new information, such as new hazard or exposure data or information on changes to the use pattern, which would affect the cumulative risk assessment. Should the Agency determine that new information on glyphosate is available that could potentially impact the cumulative risk assessment and result in a risk of concern, the Agency will revisit the cumulative risk assessment.

## **Human Studies**

No human studies have been used and relied upon for a regulatory decision on glyphosate.

## **Data Requirements**

### *Toxicology*

An immunotoxicity, acute neurotoxicity, and subchronic neurotoxicity studies, which are now required as part of revised 40 CFR Part 158, should be submitted for glyphosate to support registration review.

The following toxicology studies have been submitted are still in the process of being reviewed. Once the review has been completed, the study reviews need to be added to IHAD. The information presented in these studies will be taken into account for the final registration review of glyphosate.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

- 47311001 Mackenzie, S.; Shen, A (2007) IN-MCX20: Subchronic Toxicity 90-Day Feeding Study in Rats. Project Number: DUPONT/19008, 16394, 1026. Unpublished study prepared by Dupont CropScience. 21 p.
- 47311004 Wagner, V.; Klug, M. (2007) IN-EY252: Bacterial Reverse Mutation Assay. Project Number: AB47BT/503/BTL, 17186, 28057. Unpublished study prepared by Bioreliance. 71 p.

*Residue Chemistry*

The following studies were requested (Memo, T. Bloem, 18-Mar-08, D345923; and Memo, T. Bloem, 29-Oct-08, D357880), and are still outstanding:

- Nature of the Residue - Plants: The petitioner is requested to submit the full Optimum™ GAT™ soybean metabolism study as specified in 860.1300.
- Nature of the Residue - Livestock: The petitioner is requested to submit the ruminant and poultry metabolism studies referenced in the livestock method validation study (MRID 47311011; dosed with <sup>14</sup>C-*N*-acetyl-glyphosate).
- Meat, Milk, Poultry, and Eggs: The petitioner is requested to submit the ruminant and poultry feeding studies referenced in the livestock validation study (MRID 47311011; dosed with *N*-acetyl-glyphosate).

*Occupational and Residential Exposure*

No new occupational exposure or residential exposure data requirements have been identified for glyphosate to support registration review.

**References**

Author	Barcode	Date	Title
The Agricultural Health Study			<a href="http://aghealth.nci.nih.gov/index.html">http://aghealth.nci.nih.gov/index.html</a>
T. Bloem	D253421	25-Feb-99	PP#2F04886. Glyphosate in/on Glyphosate-Tolerant Sugar Beets. HED Risk Assessment.
T. Bloem	D349696	5-Mar-08	Glyphosate. Section 3 Registration for Application to Transgenic Soybean. Request for Petition Method Validation (PMV).
T. Bloem	D346713, D349700, D349729	12-Mar-08	Petition: 6F7146. Glyphosate-Isopropylammonium and Pyriithiobac Sodium. Application to Glyphosate-Tolerant Soybeans. Summary of Analytical Chemistry and Residue Data.
T. Bloem	D348927; D348928	2-Sep-08	Glyphosate. Label Amendment to Permit Application of Glyphosate to Bayer's Glyphosate-Tolerant Cotton GHB614.
T. Bloem	D357880	29-Oct-08	Glyphosate and Pyriithiobac Sodium. Amended Section 3 Registration to Permit the Rotation to Glyphosate-Tolerant Field Corn and Glyphosate-Tolerant Soybean Following

## Glyphosate Registration Review Human-Health Assessment Scoping Document

Table 2. Memoranda Relevant to Registration Review.			
Author	Barcode	Date	Title
			Application to Glyphosate-Tolerant Cotton and Revision of the Field Corn Tolerance Expression. Summary of Analytical Chemistry and Residue Data.
T. Bloem, PV Shah	D345923; D348895	18-March-2008	Petition: 6F7146. Glyphosate-Isopropylammonium and Pyriithiobac Sodium. Human-Health Risk Assessment for Application to Glyphosate-Tolerant Soybean.
T. Bloem, Chemist	D357880	29-Oct-08	Glyphosate and Pyriithiobac Sodium. Amended Section 3 Registration to Permit the Rotation to Glyphosate-Tolerant Field Corn and Glyphosate-Tolerant Soybean Following Application to Glyphosate-Tolerant Cotton and Revision of the Field Corn Tolerance Expression. Summary of Analytical Chemistry and Residue Data.
T. Bloem	D242628, D245591	30-Nov-98	PP# 2E04118 (formerly 2H05650) - Glyphosate residues in/on glyphosate tolerant canola seed and canola meal. Amendment of 24-August-1998.
A.J. De Roos, A. Blair, J.A. Rusiecki, J.A. Hoppin, M. Svec, M.Dosemeci, D.P. Sandler, M.C. Alavanja	N/A	Jan-05	Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study. Environmental Health Perspectives 113:49-54.
W. Donovan, W. Dykstra, M. Christian,	D267588	17-Aug-00	PP#s 9F05096; 9F06007; 8F04973; 9E06003; and ID# 00ND0025. Glyphosate in/on Alfalfa Hay and Forage; Field Corn Forage; Stover and Straw of the Cereal Grains Crop Group; Numerous Minor Crops; and Flax in North Dakota. HED Risk Assessment.
W. Donovan	D280830	15-Feb-02	Chronic Dietary Exposure Assessment for the Risk Assessment of Glyphosate; PC codes 417300 & 103601; DP Barcode D280830; Case 292955; Submission S579658.
W. Donovan	D280830	15-Feb-02	Chronic Dietary Exposure Assessment for the Risk Assessment of Glyphosate; PC codes 417300 & 103601; DP Barcode D280830; Case 292955; Submission S579658.
W. Donovan, W. Dykstra, J.T. Swackhammer	D280831	20-Feb-02	PP#s 0F06130, 0F06195, and 0F06273. Glyphosate in/on Pasture and Rangeland Grasses, Roundup Ready® Wheat, and Nongrass Animal Feeds. Health Effects Division (HED) Risk Assessment. Barcode D280831. PC Codes 103601 & 417300. Case 292955. Submission S579658.
W. Dykstra, Z. Ghali	TXR 000897	30-Oct-91	Second Peer Review of Glyphosate.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

<b>Table 2. Memoranda Relevant to Registration Review.</b>			
<b>Author</b>	<b>Barcode</b>	<b>Date</b>	<b>Title</b>
W. Dykstra, J. Rowland	TXR012586	20-Apr-98	Glyphosate- Report of the Hazard Identification Assessment Review Committee.
M. Hawkins	N/A	12-Mar-09	Updated Review of Glyphosate Incident Reports.
G.F. Kramer	D311356	19-May-05	Residues of Concern in Transgenic Glyphosate-Tolerant Crops. PC Code 103601. DP# 311356. Decision# 351808.
G.F. Kramer	D217539	14-Mar-96	PP# 5F04555. Glyphosate in or on Corn Forage. Evaluation of Residue Data and Analytical Methods. MRID#s 437127-01 & -02. Chemical 103601. Barcodes D217539 & D217541. CBTS#s 15913 & 15914.
R.B. Perfetti	N/A	17-Mar-94	Decision: The Metabolism Committee Meetings for Glyphosate Held on March 17, 1994.
R.B. Perfetti	N/A	11-Aug-92	Briefing: To Be Presented to the HED Metabolism Committee At The Meeting of August 19, 1992: Glyphosate Regulations and Codex Harmonization.
R.B. Perfetti	N/A	19-Aug-92	Decision: The Metabolism Committee Meetings for Glyphosate Held on August 19, 1992.
R.B. Perfetti	N/A	2-Mar-94	Briefing: To Be Presented to the HED Metabolism Committee At The Meeting of March 9, 1994: Glyphosate/AMPA Regulation.
R.B. Perfetti	D183202	27-Oct-92	Glyphosate: List A Reregistration Case No. 0718: Product and Residue Chemistry Chapters for the Reregistration Eligibility Document (RED). CBRS No. 10,665, DP Barcode No. D183202.
J.T. Swackhammer	D281503	13-Mar-02	Occupational (and Updated Non-Occupational and Residential) Exposure Risk Assessment for the Use of Glyphosate, Isopropylamine salt on Alfalfa, Clover and other Forage Legumes, Roundup Ready® Wheat and Corn, Grass forage, Fodder, and Hay. PC Code: 103601; DP Barcode: D281503.
J.T. Swackhammer	D281884	4-Apr-02	Amendment to HED Risk Assessment, Glyphosate in/on Pasture and Rangeland Grasses, Roundup Ready® Wheat, and Nongrass Animal Feeds, PC Codes 103601 & 417300. Case 292955. Submission S579658. Barcode D281884.
B. Tarplee, J. Rowland	TXR012584	17-Apr-98	Glyphosate – Report of the FQPA Safety Factor Committee.
J.R. Tomerlin	D321992	29-Sep-06	Glyphosate Human Health Risk Assessment for Proposed Use on Indian Mulberry and Amended Use on Pea, Dry. PC Code: 417300, Petition No: 5E6987, DP Num: 321992, Decision No. 360557.
J.R. Tomerlin	D321667	6-May-06	Glyphosate: Safflower and Sunflower; Summary of Analytical Chemistry and Residue Data. Petition Number 4E6878.

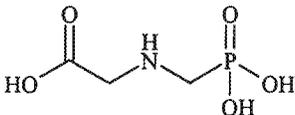
## Glyphosate Registration Review Human-Health Assessment Scoping Document

<b>Table 2. Memoranda Relevant to Registration Review.</b>			
<b>Author</b>	<b>Barcode</b>	<b>Date</b>	<b>Title</b>
J.R. Tomerlin	D321666	8-May-06	Glyphosate: Chronic Dietary Exposure Assessment for the Section 3 Registration Action.
J.R. Tomerlin	D314255, D327313	13-Jun-06	Glyphosate: Coffee; Summary of Analytical Chemistry and Residue Data. Request to Amend WeatherMAX® Label to Lower the PHI to One Day.
J.R. Tomerlin	D314476	5-Sep-06	Glyphosate Human Health Risk Assessment for Proposed Uses on Safflower and Sunflower. PC Code: 103601, Petition No: 4E6878, DP Num: 314476.
J. R. Tomerlin	D322410	26-Sep-06	Glyphosate. Petition for the Establishment of a Permanent Tolerance for Use on Indian Mulberry and Request to Amend Use on Dry Pea. Summary of Analytical Chemistry and Residue Data. PP#5E6987.
	EPA 738-R-93-014	XX-Sep-93	Reregistration Eligibility Decision (RED) Document: Glyphosate,

**Attachments****Attachment 1: Chemical Identity Table****Attachment 3: Exposure Potential for Adult and Child Short-term Aggregate Risk Estimates****Attachment 4: International Residue Limit Status****Attachment 5: DCI Justification for Acute and Subchronic Neurotoxicity Studies****Attachment 6: DCI Justification for Immunotoxicity Studies****Attachment 7: DCI Justification for Immunotoxicity Studies**

## Glyphosate Registration Review Human-Health Assessment Scoping Document

## Attachment 1: Chemical Identity Table

Table 3. Chemical Identity of Glyphosate.	
Common Name	Glyphosate
Chemical Name	<i>N</i> -(phosphonomethyl)glycine
PC Codes	103601 – glyphosate isopropylamine salt 103603 – sodium glyphosate 103604 – glyphosate monoammonium salt 103605 – glyphosate ethanolamine salt 103607 – glyphosate diammonium salt 103608 – glyphosate dimethylammonium salt 103613 – potassium glyphosate 417300 – glyphosate; free acid
Chemical Abstracts No.	38641-94-0, 70393-85-0, 40465-66-5, ?, 69254-40-6, 34494-04-7, 70901-20-1, 1071-83-6
Registration Review Case No.	0178
Chemical Class	Phosphanoglycine herbicide
Chemical Structure	 <chem>OC(=O)CNCP(=O)(O)O</chem>

## Glyphosate Registration Review Human-Health Assessment Scoping Document

## Attachment 2: Glyphosate Endpoint Selection Tables

Table 4. Summary of Toxicological Doses and Endpoints for Glyphosate for Use in Human-health Risk Assessments <sup>1</sup> .			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary, Females 13-49 and all segments of the general population	None	None	An acute dietary endpoint was not selected for the general population or females 13-50, since an appropriate endpoint attributable to a single exposure was not identified in the toxicology data base.
Chronic Dietary (all populations)	NOAEL= 175 mg/kg/day UF = 100 Chronic RfD = 1.75 mg/kg/day	FQPA SF = 1x cPAD = cRfD  cPAD = 1.75 mg/kg/day	Developmental Toxicity Study - rabbit LOAEL = 350 mg/kg/day based on diarrhea, nasal discharge and death in maternal animals
Short-, and Intermediate-Term Incidental, Oral (Residential)	NOAEL = 175 mg/kg/day	LOC for MOE = 100	Developmental Toxicity Study - rabbit LOAEL = 350 mg/kg/day based on diarrhea, nasal discharge and death in maternal animals
Short-, Intermediate- and Long-Term Dermal (1 - 30 days, 1-6 months, 6 months-lifetime) (Occupational/Residential)	None	None	Based on the systemic NOAEL of 1,000 mg/kg/day in the 21 day dermal toxicity study in rabbits and the lack of concern for developmental and reproductive effects, the quantification of dermal risks is not required.
Short-, Intermediate- and Long-Term Inhalation (1-30 days, 1- 6 months, 6 months-lifetime) (Occupational/Residential)	None	None	Based on the systemic toxicity NOAEL of 0.36 mg/L (HDT) in the 28-day inhalation toxicity study in rats, and the physical characteristics of the technical (wetcake), the quantification of inhalation risks is not required.
Cancer (oral, dermal, inhalation)	<b>Classification:</b> Group E; no evidence of carcinogenicity; risk assessment not required.		

<sup>1</sup> UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no-observed adverse-effect level, LOAEL = lowest-observed adverse-effect level, PAD = population-adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, HDT = highest dose tested.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**Attachment 3: Exposure Potential for Adult and Child Short-term Aggregate Risk Estimates**

Exposure Scenario		Exposure (Dose) mg ai/kg bw/day	MOE	Combined Exposure (Dose) mg/kg/day <sup>2</sup>	Combined MOE <sup>3</sup>
Toddler – Treated Turf <sup>4</sup>	Incidental oral hand-to-mouth post-application exposure from contacting treated turf	0.0242	7,230	0.03025	5,800
	Incidental oral post-application exposure from ingestion of treated soil	$8.13 \times 10^{-5}$	>10 <sup>6</sup>		
	Incidental oral post-application exposure from object-to-mouth	0.00605	28,900		
Toddler – Swimmer	Incidental oral post-application exposure from contacting treated water	0.023	7,610	--	--
Adult – Swimmer	Incidental oral post-application exposure from contacting treated water	0.00493	35,500	--	--

<sup>1</sup> Source of information: Memo, J.R. Tomerlin, 29-Sep-06, D321992.

<sup>2</sup> Combined exposure (dose) (mg/kg/day) = Dose<sub>Hand-to-mouth</sub> + Dose<sub>soil ingestion</sub> + Dose<sub>Object-to-mouth</sub>.

<sup>3</sup> Combined MOE = NOAEL (175 mg/kg/day) / Combined exposure (dose) (mg/kg/day).

<sup>4</sup> The residential exposures will change based on the new residential use product (EPA Reg. No. 71995-25) which higher rate of application (10.5 lb ae/A); however the increased application rate is not expected to lead to exposures which exceed HED's level of concern for residential exposures (MOEs <100). The new residential exposure risk assessment will reflect the change in rate of application.

**Attachment 4: International Residue Limit Status**

U.S.	Canada	Mexico <sup>1</sup>	Codex	
<b>Residue Definition:</b>				
40CFR180.364 glyphosate <i>N</i> -phosphonomethylglycine resulting from the application of glyphosate, the isopropylamine salt of glyphosate, the ethanolamine salt of glyphosate, the dimethylamine salt of glyphosate, the ammonium salt of glyphosate, and the potassium salt of glyphosate.	<i>N</i> - (phosphonomethyl) glycine, including the metabolite amino methylphosphonic acid (AMPA)	Glyphosate	#158 For compliance with MRLs in plant and animal commodities: Glyphosate.	
<b>Commodity Tolerance (ppm) /Maximum Residue Limit (mg/kg)</b>				
Commodity	U.S.	Canada	Mexico	Codex
Acerola	0.2			
Alfalfa, seed	0.5			
Almond, hulls	25			
Aloe vera	0.5			
Ambarella	0.2			

## Glyphosate Registration Review Human-Health Assessment Scoping Document

Table 6. Summary of U.S. Tolerances and International MRLs.				
U.S.		Canada	Mexico <sup>1</sup>	Codex
Animal feed, nongrass, group 18	400			Alfalfa fodder 500 Bean fodder 200 Pea hay or pea fodder (dry) 500
Artichoke, globe	0.2		0.2	
Asparagus	0.5	0.5		
Atemoya	0.2			
Avocado	0.2		0.2	
Bamboo, shoots	0.2			
Banana	0.2		0.2	0.05 <sup>4</sup>
Barley, bran	30			
Beet, sugar, dried pulp	25			
Beet, sugar, roots	10	10		
Beet, sugar, tops	10			
Berry group 13	0.2			
Betelnut	1.0			
Biriba	0.2			
Blimbe	0.2			
Borage, seed	0.1			
Breadfruit	0.2			
Cacao bean	0.2		0.2	
Cactus, fruit	0.5			
Cactus, pads	0.5			
Canistel	0.2			
Canola, seed	20	10		Rape seed 20
Cattle, meat byproducts	5.0	Kidney 2 Liver 0.2		Edible offal (mammalian) 5
Chaya	1.0			
Cherimoya	0.2			
Citrus, dried pulp	1.5			
Coconut	0.1			
Coffee, bean	1.0		1	
Corn, field, forage	6.0			
Corn, field, grain	5.0	3	0.1	Maize 5
Corn, pop, grain	0.1			
Corn, sweet, grain	0.1			
Cotton, gin byproducts	175			
Cotton, undelinted seed	40		15	40
Cranberry	0.2			
Crambe, seed	0.1			
Custard apple	0.2			
Date	0.2			
Dokudami	2.0			
Durian	0.2			

## Glyphosate Registration Review Human-Health Assessment Scoping Document

<b>Table 6. Summary of U.S. Tolerances and International MRLs.</b>				
<b>U.S.</b>		<b>Canada</b>	<b>Mexico<sup>1</sup></b>	<b>Codex</b>
Egg	0.05			0.05 <sup>4</sup>
Epazote	1.3			
Feijoa	0.2			
Fig	0.2			
Fish	0.25			
Flax, meal	8.0			
<b>Flax, seed</b>	<b>4.0</b>	<b>3</b>		
<b>Fruit, citrus, group 10</b>	<b>0.5</b>		Lime 0.5 Lemon 0.2 Mandarin 0.5 Orange 0.2 Grapefruit 0.2 Tangerine 6	
Fruit, pome, group 11	0.2		Apple 0.2 Pear 0.2	
Fruit, stone, group 12	0.2		Apricot 0.2 Plum 0.2 Peach 0.2	
Galangal, roots	0.2			
Ginger, white, flower	0.2			
<b>Goat, meat byproducts</b>	<b>5.0</b>	<b>Kidney 2 Liver 0.2</b>		Edible offal (mammalian) 5
Gourd, buffalo, seed	0.1			
Governor's plum	0.2			
Gow kee, leaves	0.2			
Grain, aspirated fractions	100			
<b>Grain, cereal, forage, fodder and straw, group 16, except field corn, forage</b>	<b>100</b>			<b>Barley straw and fodder (dry) 400</b> Oat straw and fodder (dry) 100 Sorghum straw and fodder (dry) 50 Wheat straw and fodder (dry) 300

## Glyphosate Registration Review Human-Health Assessment Scoping Document

<b>Table 6. Summary of U.S. Tolerances and International MRLs.</b>				
<b>U.S.</b>		<b>Canada</b>	<b>Mexico<sup>1</sup></b>	<b>Codex</b>
<b>Grain, cereal, group 15 except field corn, popcorn, rice, sweet corn, and wild rice</b>	<b>30</b>	<b>Barley 10 Oats 15 Wheat 5</b>	<b>Rice 0.1 Oats 0.1 Barley 0.1 Rye 0.1 Sorghum 0.1 Wheat 5 Corn 0.1</b>	<b>Cereal grains 30 (except maize)</b>
Maize fodder (dry)				150
Grape	0.2		0.2	
<b>Grass, forage, fodder and hay, group 17</b>	<b>300</b>		<b>Alfalfa 200 Grass (pasture) 200</b>	<b>Hay or fodder of grasses (dry) 500</b>
Guava	0.2		0.2	
Herbs subgroup 19A	0.2			
<b>Hog, meat byproducts</b>	<b>5.0</b>	<b>Kidney 2 Liver 0.2</b>		<b>??Edible offal 0.5<sup>2</sup></b>
Hop, dried cones	7.0			
Horse, meat byproducts	5.0			Edible offal (mammalian) 5
Ilama	0.2			
Imbe	0.2			
Imbu	0.2			
Jaboticaba	0.2			
Jackfruit	0.2			
Joboba, seed	0.1			
Juneberry	0.2			
Kava, roots	0.2			
Kenaf, forage	200			
Kiwifruit	0.2			
Lesquerella, seed	0.1			
Leucaena, forage	200			
Lingonberry	0.2			
Longan	0.2			
Lychee	0.2			
Mamey apple	0.2			
Mango	0.2		0.2	
Mangosteen	0.2			
Marmaladebox	0.2			
Meadowfoam, seed	0.1			
Mioga, flower	0.2			
<b>Mustard, seed</b>	<b>0.1</b>		<b>0.2</b>	

## Glyphosate Registration Review Human-Health Assessment Scoping Document

<b>Table 6. Summary of U.S. Tolerances and International MRLs.</b>				
<b>U.S.</b>		<b>Canada</b>	<b>Mexico<sup>1</sup></b>	<b>Codex</b>
Noni	0.20			
Nut, pine	1.0			
Nut, tree, group 14	1.0		Walnut 1	
Okra	0.5			
Olive	0.2			
Oregano, Mexican, leaves	2.0			
Palm heart	0.2			
Palm heart, leaves	0.2			
Palm, oil	0.1			
Papaya	0.2		0.2	
Papaya, mountain	0.2			
Passionfruit	0.2			
Pawpaw	0.2			
Pea, dry <sup>3</sup>	8.0 <sup>3</sup>	5.0 (dry?)	0.2 (dry?)	5
Peanut	0.1		0.1	
Peanut, hay	0.5			
Pepper leaf, fresh leaves	0.2			
Peppermint, tops	200			
Perilla, tops	1.8			
Persimmon	0.2			
Pineapple	0.1			
Pistachio	1.0			
Pomegranate	0.2			
Poultry, meat	0.1			0.05 <sup>4</sup>
Poultry, meat byproducts	1.0	Kidney 2 Liver 0.2		Poultry edible offal 0.5
Pulasan	0.2			
Quinoa, grain	5.0			
Rambutan	0.2			
Rapeseed, seed	20			
Rice, grain	0.1		0.1	
Rice, wild, grain	0.1			
Rose apple	0.2			
Safflower, seed	85			
Salal	0.2			
Sapodilla	0.2			
Sapote, black	0.2			
Sapote, mamey	0.2			
Sapote, white	0.2			
Sesame, seed	0.1			
Sheep, meat byproducts	5.0	Kidney 2 Liver 0.2		Edible offal (mammalian) 5
Shellfish	3.0			
Soursop	0.2			
Soybean, forage	100			
Soybean, hay	200			
Soybean, hulls	100			

## Glyphosate Registration Review Human-Health Assessment Scoping Document

<b>Table 6. Summary of U.S. Tolerances and International MRLs.</b>				
<b>U.S.</b>		<b>Canada</b>	<b>Mexico<sup>1</sup></b>	<b>Codex</b>
Soybean, seed	20	20	6	20
Spanish lime	0.2			
Spearmint, tops	200			
Spice subgroup 19B	7.0			
Star apple	0.2			
Starfruit	0.2			
Stevia, dried leaves	1.0			
Strawberry	0.2			
Sugar apple	0.2			
Sugarcane, cane	2.0		2	2
Sugarcane, molasses	30			10
Sunflower, seed	85			7
Surinam cherry	0.2			
Tamarind	0.2			
Tea, dried	1.0			
Tea, instant	7.0			
Teff, grain	5.0			
Ti, leaves	0.2			
Ti, roots	0.2			
Ugli fruit	0.5			
Vegetable, bulb, group 3	0.2		Garlic 0.2 Onion 0.2	
Vegetable, cucurbit, group 9	0.5		Pumpkin 0.5 Watermelon 0.5 Cucumber 0.5 Melon 0.5	
Vegetable, foliage of legume, subgroup 7A, except soybean	0.2			
Vegetable, fruiting, group 8	0.1		Eggplant 0.1 Non-bell pepper 0.1 Tomato 0.1	
Vegetable, leafy, brassica, group 5	0.2		Broccoli 0.2 Cauliflower 0.2	

## Glyphosate Registration Review Human-Health Assessment Scoping Document

<b>Table 6. Summary of U.S. Tolerances and International MRLs.</b>				
<b>U.S.</b>		<b>Canada</b>	<b>Mexico<sup>1</sup></b>	<b>Codex</b>
Vegetable, leafy, except brassica, group 4	0.2		Spinach 0.2 Celery 0.2 Lettuce 0.2 Swiss chard 0.2	
Vegetable, leaves of root and tuber, group 2, except sugar beet tops	0.2			
Vegetable, legume, group 6 except soybean and dry pea	5.0	Beans 4.0 Lentils 4.0	Bean 0.2	Beans (dry) 2
Vegetable, root and tuber, group 1, except sugar beet	0.2		Carrot 0.2 Potato 0.2 Radish 0.2 Beet 0.2	
Wasabi, roots	0.2			
Water spinach, tops	0.2			
Watercress, upland	0.2			
Wax jambu	0.2			
Yacon, tuber	0.2			
Meat (from mammals other than marine mammals)				0.05 <sup>4</sup>
Milks				0.05 <sup>4</sup>
Wheat bran, unprocessed				20
Barley milling fractions, excluding flour		15		
Oats milling fractions, excluding flour		35		
Wheat milling fractions, except flour		15		
Chayote			0.5	

<sup>1</sup> As of 2004, latest date for available information. General practice is for Mexico to defer to US or Codex tolerances for its export purposes.

<sup>2</sup> Probable editorial error. No data to indicate derivation. Most likely is 5.

<sup>3</sup> See legume vegetables.

<sup>4</sup> Absent at the limit of quantitation.

**Attachment 5: DCI Justification for Acute and Subchronic Neurotoxicity Studies**

<b>Guideline Number: 870.6200</b>
<b>Study Title: Acute and Subchronic Neurotoxicity</b>
<b>Rationale for Requiring the Data</b>
<p>This is a data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).</p> <p>The Neurotoxicity Test Guideline (OPPTS 870.6200) prescribes functional and structural neurotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects on the nervous system. Although some information on neurotoxicity may be obtained from standard guideline toxicity study data, studies not specifically conducted to assess neurotoxic endpoints may be inadequate to characterize a pesticide's potential neurotoxicity. While data on clinical signs of toxicity or histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential neurotoxic effects, these endpoints alone may be insufficient to detect more subtle neurological effects.</p>
<b>Practical Utility of the Data</b>
<p><b>How will the data be used?</b></p> <p>Neurotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the nervous system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures of glyphosate on neurologic parameters are nonexistent, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation.</p> <p><b>How could the data impact the Agency's future decision-making?</b></p> <p>If the neurotoxicity studies show that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.</p> <p>If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.</p>

**Attachment 6: DCI Justification for Immunotoxicity Studies**

<b>Guideline Number: 870.7800</b>
<b>Study Title: Immunotoxicity</b>
<b>Rationale for Requiring the Data</b>
<p>This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).</p> <p>The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.</p>
<b>Practical Utility of the Data</b>
<p><b>How will the data be used?</b></p> <p>Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).</p> <p><b>How could the data impact the Agency's future decision-making?</b></p> <p>If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.</p> <p>If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.</p>

**Attachment 7: DCI Justification for Immunotoxicity Studies**



**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460**

**OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES**

March 12, 2009

**MEMORANDUM**

**SUBJECT:** Updated Review of Glyphosate Incident Reports

**FROM:** Monica Hawkins, M.P.H., Environmental Health Scientist  
Toxicology and Epidemiology Branch  
Health Effects Division (7509P)

Jessie Cordova, Information Technology Specialist  
Toxicology and Epidemiology Branch  
Health Effect Division (7509P)

**THRU:** Mary Manibusan, Branch Chief  
Toxicology and Epidemiology Branch  
Health Effects Division (7509P)

**TO:** John Pates, CRM  
Special Review and Reregistration Division (7508P)

**BACKGROUND**

The OPP Incident Data System (IDS) was consulted for poisoning incident data on the active ingredient glyphosate. The purpose of the database search is to identify potential patterns on the extent and severity of the health effects attributed to glyphosate exposure. The IDS includes reports of incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6 (a) (2) reports from registrants, other federal and state health and environmental agencies and individual consumers. The following databases were not searched for poisoning incident data: the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), the California Pesticide Illness Surveillance Program, and the National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR). The EPA is supplying the following incident report to fulfill our requirement to docket summaries of incident data that were reported

to the Agency. This report represents 289 incidents occurring in the United States from 2002 to the present for the single chemical only.

Reports of adverse health effects allegedly due to a specific pesticide exposure (an “incident”) is largely self-reported and therefore, generally speaking, neither exposure to a pesticide or reported symptom (or the connection between the two) is validated. However, incident information can be an important feedback loop to the Agency – incidents of severe outcome, or a suggested pattern or trend among less severe incidents can signal the Agency to further investigate a particular chemical or product.

The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) includes reports of alleged human health incidents from various sources, including mandatory reports from registrants, other federal and state health and environmental agencies and individual consumers. Since 1992, OPP compiles these reports in an Incident Data System (IDS). Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in this report. Typically, OPP does not draw firm conclusions implicating the pesticide is causally associated with the reported health effects. Nevertheless, in some instances if enough cases and/or documentation of exposure and health effect or suggested patterns of exposure and response are indicative of a strong relationship, risk mitigation measures may be suggested.

In this evaluation, we identified 289 glyphosate case reports allegedly attributable to the organophosphate glyphosate reported to the IDS between 2002 and 2008. We reviewed the written content of each summarized case-report to determine the health effects most commonly allegedly associated with glyphosate use/exposure. Based on the IDS, we identified 8 major types of adverse health effects: gastro-intestinal (4.8%), dermal (30.1%), upper-respiratory (10.3%), neurological (34.3%), cardiovascular (0.3%), ocular (13.8%), muscular (0.3%), and combination (5.5%) effects. Only 2 case reports (0.7%) alleged exposure with no symptoms reported. Disturbances of the gastrointestinal and neurological systems are congruent with classic organophosphate exposure within the GI system. Among the case reports, gastrointestinal effects reported included diarrhea, abdominal cramps, stomach pain. Neurological system effects included shaking, loss of coordination, tingling, neuropathy, ataxia, and numbness. Dermal effects included blisters, rash, pruritus, skin irritation, hives, welts, sores, burning skin, and peeling skin. Many of the dermal cases are associated with splashing of the product that leaked onto hands. Among the case reports, the majority of the reported symptoms involved dermal and neurological effects.

Glyphosate exhibits low toxicity via the oral, dermal, and inhalation routes (Toxicity Category III or IV). Glyphosate exhibits only a mild eye irritation and slight dermal irritation and is not a skin irritant or sensitizer. In general, glyphosate is a moderately toxic insecticide and the IDS query resulted in a moderately large number of case reports which warrants searching the following databases for consistency and reproducibility of the poisoning incident data: the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), the California Pesticide Illness Surveillance Program, and the National Institute of Occupational Safety and Health’s Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR).

Glyosate Registration Review Human-Health Assessment Scoping Document

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Symptoms	Frequency (%)
Dermal	87 (30.1)
Gastro-intestinal	13 (4.8)
Upper Respiratory	30 (10.3)
Neurological	99 (34.3)
Combination	16 (5.5)
Ocular	40 (13.8)
Muscular	1 (0.3)
Cardiovascular	1 (0.3)
No Symptoms	2(0.7)
Total	100% <sup>1</sup>

<sup>1</sup>overall frequency does not total 100% due to rounding.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
012676	001	21-Feb-02	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		FL	HC	Man was pouring some of the product into his own sprayer and got some of the product on top of his hand. Unknown Adult (18-64 years old) Male reported Water Blisters and Redness.
012776	001	01-Mar-02	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		CA	HC	Unknown Adult (18-64 years old) Female mixed the product with water and a small amount of the diluted product splashed into her eye. She reported Eye Redness, Irritation/Pain, and Superficial Corneal Abrasion.
012776	002	16-Mar-02	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		VA	HC	Unknown Adult (18-64 years old) Male sprayed the product and the hose stretched away from the bottle and it broke off spraying him in the Face, Eye, and Nose. He reported Eye Irritation, Swollen, Redness, Difficulty Breathing, and Dizziness.
12852	002	09-Apr-02	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		LA	HC	Unknown Adult (18-64 years old) Male used the diluted product while it was windy. Some of the product got into his eye or he rubbed his eye and scratched it. He reported Eye Irritation, Redness.
012852	003	17-Apr-02	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		GA	HC	Unknown Adult (18-64 years old) Male got some of the diluted product in his eyes. He reported Irritation/Pain, Redness.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report**

3/12/09

**Chemical: Glyphosate****103601****Human Incidents**

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
012852	004	27-Apr-02	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		NJ	HC	Unknown Adult (18-64 years old) Male sprayed the diluted product and the sprayer blew some of the product in his eyes and all over his body. He reported Ocular Irritation, Blurred Vision.
12854	001	17-Apr-02	KLEERAWAY GRASS & WEED KILLER 1 READY-TO-USE	07199500010	HARRISBURG	PA	HC	Unknown Adult (18-64 years old) Female reported Redness, Irritation after some of the product sprayed her in her eyes.
013090	001	15-Jun-02	GLYFOS X-TRA HERBICIDE	00478700023	SHEBOYGAN	WI	HC	Unknown Adult (18-64 years old) Female was possibly exposed during application of the product to farm crops. She reported Rash, Blisters from working in treated soil.
013105	001	13-Jun-02	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		IN	HC	Unknown Adult (18-64 years old) Male sprayed a large area with the product and got a fair amount on his skin. On the same day the sprayer leaked on his left leg and soaked through his pants. He reported Rash, Redness, and Pruritus.
013105	002	18-Jun-02	ROUNDUP ULTRA MAX	00052400512		SC	HC	Unknown Adult (18-64 years old) Male sprayed the product with a spray gun when he tested the line. Some of the product sprayed into his eye. He reported Ocular Irritation, Redness.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
013181	001	08-Jul-02	ROUNDUP WEED AND GRASS KILLER READY TO USE FROM MONSANTO	07199500023		MI	HC	Unknown Adult (18-64 years old) Male, who has a landscaping business, got some of the product into his right eye. He was diagnosed with Corneal Abrasion.
013181	002	12-Jul-02	ROUNDUP WEED AND GRASS KILLER READY TO USE FROM MONSANTO	07199500008		WV	HC	Unknown Adult (18-64 years old) Female used the product. After she pulled on one of the pieces of equipment it flew in the air and hit her hand and caused an abrasion. She reported Skin Irritation.
013181	003	25-Jul-02	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE FROM MONSANTO	07199500025		GA	HC	Unknown Adult (18-64 years old) Female mixed the product and some of it splashed into her eyes. She reported Burning Eyes.
013181	004	26-Jul-02	ROUNDUP WEED & GRASS KILLER CONCENTRATE FROM MONSANTO	07199500026		FL	HC	Unknown Adult (18-64 years old) Female used the product and some of it splashed into her eye. She reported Ocular Irritation, Redness.
013203	001	24-May-02	GLYFOS X-TRA	00478700023	YADKINVILLE	NC	HD	Unknown Adult (18-64 years old) Female reported Rash, Pruritus after some of the product blew into the air.
013223	001	17-Aug-02	PROSECUTOR	00022800366 010404			HB	Unknown Adult (18-64 years old) Male used a backpack sprayer to spray weeds in his backyard. Wore t-shirt & shorts, no shoes. Was later found passed out. No Symptoms Described.
013243	033	11-Jul-02	GROUND CLEAR COMPLEX VEGETATION KILLER (CONCENTRATE)	00023902657	MINNEAPOLIS	MN	HC	Unknown Adult (18-64 years old) Female reported Rash, Pruritus after using the product.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

## IDS Report

3/12/09

Chemical: Glyphosate

103601

Human Incidents

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
013263	001	03-Aug-02	ROUNDUP W&G KILLER RTU	07199500023		ID	HC	A Man cleaned out a container and some of the product splashed into his right eye. Unknown Adult (18-64 years old) Male reported Irritation/Pain.
013263	002	07-Aug-02	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		KS	HC	Unknown Adult (18-64 years old) Male reported Ocular Irritation, Dermal Irritation. He tried to open the container and it exploded in the man's Face, Eyes and Mouth.
013331	158	01-Aug-02	TRIOX LIQUID VEGETATION KILLER	00023902657	SAN FRANCISCO	CA	HC	Unknown Adult (18-64 years old) Female says that the neighbor sprayed the product and she can smell. No Symptoms Mentioned.
013386	003	18-Aug-02	GLYPRO (NAF-552)	06271900324	HELVETIA	WV	HC	A 72 year old Male reported Renal Failure, Dysphagia when the diluted product was sprayed near his farm.
013391	001	25-Sep-02	ROUNDUP WEED & GRASS KILLER	07199500025		MA	HC	Unknown Adult (18-64 years old) Female poured the product into a container to dilute it. Some of the product splashed directly into her eye. She reported Burning, Redness.
013391	002	28-Sep-02	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		AL	HC	Unknown Adult (18-64 years old) Female. Some of the diluted product splashed into her left eye as she poured it into the container. She reported Irritation/Pain, Redness.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
013658	001	27-Dec-02	ROUNDUP ULTRA	00052400475		HI	HC	A wife sprayed the diluted product. Her husband walked behind her and was used a weed wacker on the area she had just sprayed. Unknown Adult (18-64 years old) Male reported Rash, Blisters, and Swelling.
013915	001	15-Jun-02	ROUNDUP W&G KILLER READY TO USE	07199500008	LA PALMA	CA	HC	Unknown Adult (18-64 years old) Male reported Nail Fungus. He used the product to kill weeds in his driveway. It took him over a half hour to complete the spraying and he noticed that the product had been coming out the trigger on the spray and dripping down his left hand.
014001	001	29-Apr-03	ROUNDUP W & G KILLER READY TO USE	07199500008		NC	HC	Unknown Adult (18-64 years old) Female employee experienced Blurred Vision & Burning Eyes after an accidental spraying near her eyes.
014039	001	09-Apr-03	GREEN THUMB CONCENTRATE WEED & GRASS KILLER	06776000059 009688	PRESCOTT	AZ	HC	Unknown Adult (18-64 years old) Female individual possibly exposed while applying product. The wind may have blown mist into the air while the product was being applied. She reported Dizziness, Weakness and Shaking.
014028	016	08-Apr-03	GROUND CLEAR SUPER EDGER PLUS KILLS PLUS PREVENTS WEEDS & GRASSES RTU	00023902516	PORTLAND	OR	HC	A 56 year old Male reported Tremor after some of the product splashed in his mouth while it was being applied.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report**

3/12/09

**Chemical: Glyphosate****103601****Human Incidents**

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
014028	021	08-Apr-03	GROUND CLEAR TRIOX TOTAL VEGETATION KILLER 1	00023902657	ROSEVILLE	CA	HC	A 40 year old Male reported Throat Irritation, Chest Pain, and Shortness of Breath after using the product 3 days earlier outside.
014068	001	29-May-03	KLEENUP PRO	00052400445 065783	OAKTON	MD	HC	A 23 year old Male reported Seizure after possible exposure to product.
014077	001	05-May-03	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		CA	HC	Approximately 2 hours earlier, a man, who was at work, got some of the diluted product into his eye. Unknown Adult (18-64 years old) Male reported Eye Irritation, Redness, and Tearing.
014197	001	30-Jun-03	HONCHO		ANTELOPE	MT	HC	Unknown Adult (18-64 years old) Female reported a Skin Rash, Breathing Problems. She rode her bicycle and a County spray truck passed her. The truck did not stop spraying and as it went by her she was drenched.
014198	072	20-Jun-03	GROUND CLEAR COMPLETE VEGETATION KILLER (CONCENTRATE)	00023902657	AURORA	CO	HC	Unknown Adult (18-64 years old) Male reported Nausea, Lethargy and Cold Sores. He used the product for the past few weeks at work.
014198	075	24-Jun-03	GROUND CLEAR TRIOX TOTAL VEGETATION KILLER 1	00023902657	DELENA	MD	HC	Unknown Adult (18-64 years old) Male reported Tremor. Product was used within the last 2 hours by a maintenance man at an apartment building. The man spoke with the maintenance man while the product was being applied.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
014219	002	01-Jun-03	GLYFOS CONCENTRATE 41% WEED AND GRASS KILLER	06776000059 009688	CRESTON	CA	HC	A 48 year old Female reported Nausea, Fever/Hyperthermia, Malaise while applying diluted product outdoors around residence area.
014313	001	21-Jun-03	NO-PEST WEED & GRASS KILLER CONCENTRATE	06776000046 009688	GREENVILLE	NC	HC	A 31 year old Male used product and some got on his hands. Product remained on his skin for one hour. He reported Edema, Hives/Welts, and Shortness of Breath.
014335	001	11-Jul-03	ROUNDUP SUPER CONCENTRATE W & G KILLER1	07199500018		NJ	HC	Man sprayed the diluted product from a pressurized sprayer. The hose came undone and the product splashed in his eyes. Unknown Adult (18-64 years old) Male reported Eye Pain, Redness.
014335	002	20-Jul-03	ROUNDUP W & G KILLER READY-TO-USE	07199500023		NY	HC	Unknown Adult (18-64 years old) Female reported a seizure.
014335	003	22-Jul-03	ROUNDUP SUPER CONCENTRATE W & G KILLER1	07199500018		NC	HC	Unknown Adult (18-64 years old) Male sprayed the product in his yard once a week. He ran the mower over the yard and he states some of the ash from burning yard waste was in air. He reported Heavy Breathing and Growly Voice.
014335	004	27-Jul-03	ROUNDUP W & G KILLER SUPER CONCENTRATE	07199500025		NC	HC	A man applied the diluted product and some of it splashed in his eyes and on his face when he lost control of the sprayer. Unknown Adult (18-64 years old) Male

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report**

3/12/09

**Chemical: Glyphosate****103601****Human Incidents**

Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
							reported Eye Burning, Irritation/Pain.
014335	005	01-May-03	ROUNDUP W & G KILLER READY-TO-USE		CA	HC	Unknown Adult (18-64 years old) Male used the product and reported with an Irregular Heartbeat and Palpitations.
014335	006	22-Jul-03	ROUNDUP W & G KILLER CONCENTRATE		CO	HC	Unknown Adult (18-64 years old) Female reported Corneal Abrasion to the Eye. She cut weeds and something blew up into her eye after the product was applied to plants.
014335	007	28-Aug-03	ROUNDUP ULTRA		PR	HC	Man used the diluted product and some of it spilled on his back and possibly splashed in his mouth. Unknown Adult (18-64 years old) Male reported Slurred Speech, Dizziness, Numb Tongue, and Loss of Coordination.
014370	001	27-Aug-03	ROUNDUP WEED & GRASS KILLER READY TO USE		VA	HC	Unknown Adult (18-64 years old) Female reported Ocular Irritation after the product splashed into her eyes.
014317	084	29-Jul-03	KGRO GRASS & WEED KILLER 19READY-TO-USE)	WILLOW STREET	PA	HC	A 64 year old Female reported Shortness of Breath, Tachycardia after she applied the product yesterday.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report**

3/12/09

**Chemical: Glyphosate****103601****Human Incidents**

Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
014372 001	20-Aug-03	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		VA	HC	A child reported Eye Irritation, Rash on Hand. The Product container was found open in a garage after the child came out of the garage.
014375 001	12-May-03	GLYFOS X-TRA HERBICIDE	00478700023	ELCO	GA	HC	A 36 year old Male reported Swelling, Edema, Chest Pain and Slurred Speech. The product may have splashed on his skin.
014375 002	18-Mar-03	GLYFOS X-TRA HERBICIDE	00478700023	SAN ANTONIO	TX	HC	A 79 year old Male reported Pain, Muscle Weakness, and Nighttime Swelling. Individual possibly exposed while applying product on a windy day.
014376 001	23-Aug-03	ROUNDUP CONCENTRATE WEED & GRASS KILLER	07199500017		NC	HC	Unknown Adult (18-64 years old) Male used the product and got some on his hands and then touched his eyes. He reported Blurred Vision.
014459 016	16-Sep-03	POWER FORCE GRASS & WEED KILLER 24 OZ RTU	06776000061 072155	STOW	OH	HC	The neighbor applied the product in his yard. He warned his neighbors that he was going to apply the product and should keep their dog and child indoors. A 6 year old Female reported Hives/Welts on her Face, Torso, Groin and Thighs.
014428 071	14-Aug-03	GROUND CLEAR COMPLETE VEGETATION KILLER (CONC)	00023902657	PARSONS	TN	HC	A 66 year Female mixed the product that splashed on her glasses and eyes. She reported Ocular Irritation/Pain, Blurred Vision.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report** 3/12/09**Chemical: Glyphosate****103601****Human Incidents**

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
014491	001	01-Jun-03	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023		MS	HC	Unknown Adult (18-64 years old) Female reported Numbness on Fingertips, Tingling after the product splashed on her hands.
014493	001	17-Oct-03	ROUNDUP HERBICIDE	00052400445		MI	HC	Unknown Adult (18-64 years old) Male carried a sack out of the store after purchasing the product that was leaking. Some of it splashed on his skin and on his stomach. He reported Rash, Blisters, Tingling and Itching.
014571	001	01-Oct-03	ROUNDUP GARDEN FOAM WEED & GRASS KILLER	07199500016		CO	HC	Unknown Adult (18-64 years old) Female used the product on weeds 4 weeks ago. Three days later she pulled the weeds. She reported Shortness of Breath, Fluid in her Lungs.
014576	001	01-Oct-03	ROUNDUP HERBICIDE	00052400445		OH	HC	Unknown Adult (18-64 years old) Female reported Rash, Red Bumps on her lower Legs. Sprayed unknown formulation of diluted product while she was wearing shorts, socks and shoes.
014578	001	01-Oct-03	ROUNDUP HERBICIDE	00052400445		ND	HC	Unknown Adult (18-64 years old) Male used the product to clear the weeds during the growing season. He reported Rash on Thumb and Middle Finger that began to spread.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report** 3/12/09**Chemical: Glyphosate****103601****Human Incidents**

Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
014579 001	01-Oct-03	ROUNDUP HERBICIDE	00052400445		ID	HC	A neighbor sprayed the product on her own property and some of the product drifted over into their neighbor's yard. Unknown Adult (18-64 years old) Male was in the yard pulling grass and planting flowers. He reported Burning Sensation to his Hands, Blisters to the Shoulders, Chest, and all over his Body.
014580 001	01-Oct-03	ROUNDUP HERBICIDE	00052400445		MO	HC	The device to attach to the hose was faulty and the product sprayed all over his Legs. Unknown Adult (18-64 years old) Male reported Tingling, Neuropathy.
014673 001	01-Nov-03	ROUNDUP HERBICIDE	00052400445		VA	HC	A Pilot applied the diluted product from an airplane on a very hot day. Unknown Adult (18-64 years old) Male reported Seizure.
014674 001	01-Nov-03	ROUNDUP HERBICIDE	00052400445		TX	HC	Unknown Adult 18-64 years old) Male spilled the product on his truck. He reported Pneumonia, Blood Clots in his Lungs.
014720 001	01-Dec-03	ROUNDUP HERBICIDE	00052400445		FL	HC	Unknown Adult (18-64 years old) Female reported Diarrhea and Blood in Stool after the product was applied near her home.
014721 001	01-Mar-03	ROUNDUP HERBICIDE	00052400445		MD	HC	A Lawn service sprayed a man's patio for weeds that grew through the bricks. Unknown Adult (18-64 years old) Male reported Shortness of Breath, Panting and Pneumonia.

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014931 001	01-Feb-04	ROUNDUP HERBICIDE	00052400445		TX	HC	A mother and her friend spraying the product. Unknown Adult (18-64 years old) Females reported Vomiting and Blood in Urine.
014962 013	20-Mar-04	POWER FORCE GRASS & WEED KILLER 1 GAL RTU	06776000061 072155	MADDERY	LA	HC	A 41 year old Male used the product and got a small amount of the product in his eye. He reported Ocular Irritation/Pain.
014968 001	01-May-03	ROUNDUP HERBICIDE	00052400445		TN	HC	Unknown Adult (18-64 years old) Male reported Sores, Pruritus, and Rash. Some of the product spilled on his pants while he used it.
015007 001	19-Mar-04	ROUNDUP HERBICIDE	00052400445		FL	HC	Unknown Adult (18-64 years old) Male used the product for about an hour. He reported Chills, Nausea and Abdominal Cramping.
015111 001	01-Apr-04	ROUNDUP RTU W&G KILLER1	07199500023		CA	HC	Unknown Adult (18-64 years old) Male used the product about 2 weeks ago. He reported Shortness of Breath and was Diagnosed with Pneumonia.
015191 001	01-May-04	ROUNDUP HERBICIDE	00052400445		NV	HC	It was windy day and a tenant in the apartment building sprayed the product. Unknown Adult (18-64 years old) Female washed her hair with the window open and dried dirt landed on top of her wet head. She reported Itching, Chemical Burn, and Nausea.
015193 001	01-May-04	ROUNDUP W & G KILLER CONCENTRATE	07199500017		CA	HC	Unknown Adult (18-64 years old) Female reported Diarrhea. The woman cleaned a sprayer that was

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
								used to spray the diluted product.
015195	001	01-May-04	ROUNDUP READY-TO-USE W&G KILLER1	07199500023		IN	HC	Unknown Adult (18-64 years old) Male released air from the sprayer bottle and some of the product splashed into his right eye. He reported Blurred Vision.
015197	001	06-May-04	ROUNDUP HERBICIDE	00052400445		GA	HC	Unknown Adult (18-64 years old) Male reported Fever, Body Aches, and Diarrhea. Some of the product may have splashed on his skin and also inhaled it.
015198	001	07-May-04	ROUNDUP ORIGINAL HERBICIDE FROM MONSANTO	00052400445		TN	HC	Unknown Adult (18-64 years old) Female sprayed the product three to four days ago. She did not use a mask on a windy day. She reported Coughing, Malaise.
015207	045	17-May-04	ORTHO BASIC SOLUTIONS WEED & GRASS KILLER CONCENTRATE	07199500006 000239	VALRICO	FL	HC	A 29 year old Male put some of the product into a sprayer and mixed it with water. When he was spraying he got some of the product on his thumb. He reported Dermal Irritation/Pain, Cold Sores.
015262	085	07-Jun-04	WEED & GRASS KILLER	07199500008	KANSAS CITY	KS	HC	Unknown Adult (18-64 years old) Male reported Rash, Skin Burning

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015317	001	01-Jun-04	ROUNDUP ORIGINAL	00052400445		MD	HC	Unknown Adult (18-64 years old) Male purchased a product and he added one quart of the product to 12 gallons of water. He sat in the back of a truck spraying the product while his wife drove. He reported Pain in his Head, and Intermittent Burning all over his Body.
015319	001	11-Aug-04	ROUNDUP W&G KILLER CONCENTRATE	07199500017		NY	HC	Unknown Adult (18-64 years old) Male used a trigger sprayer for about one hour to apply the diluted product. He states he got a small amount of the product on his hands that had some abrasions on them. He reported Tremors in his Hands.
015320	001	01-Aug-04	ROUNDUP ORIGINAL	00052400445		HI	HC	Unknown Adult (18-64 years old) Female got product on her hands and later washed them. That evening she reported Difficulty Breathing, Burning and Itching.
015322	001	03-Jun-04	ROUNDUP ORIGINAL	00052400445		PA	HC	A 6 year old boy went to play at a neighbor's house. The Father states that the child's ball went into the weeds where the product was recently applied. The boy reported Stomach Pain.
015324	001	28-Jun-04	ROUNDUP BRUSHKILLER CONCENTRATE	07199500017		AZ	HC	Unknown Adult (18-64 years old) Male sprayed the diluted product with the appropriate amount of water as listed on the label. He reported Back Pain and Blood in the Urine.

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
015321	001	25-Jun-04	ROUNDUP HERBICIDE	00052400445	HAWAII	HI	HC	Unknown Adult (18-64 years old) Male sprayed the product. The sprayer leaked on both hands 1-2 times. He reported Numbness, Swelling and Itching in Both Hands.
015372	001	12-Jul-04	CLEAROUT 41 PLUS	07082900003	WESTERN PENNSYLVANIA	PA	HC	A 16 year old Female reported working a near table where the product was spilled. She reported Inhalation, Dizziness, Shortness of Breath, Numbness, and Asthma.
015419	066	05-Jul-04	SEASON-LONG GRASS & WEED KILLER 1 GAL READY-TO-USE	00023902516	ROCKVILLE	MD	HC	Unknown Adult (18-64 years old) Female reported Headache, Nausea, 5 hours after using the product.
015495	001	01-Jul-04	ROUNDUP	00052400445		WI	HC	Someone sprayed her lawn with the product as a malicious act. A child was playing in the grass later after it was dry. One week later, a Child (3-8 years old) Reported Blue Fingertips, Lips and a Fever.
015497	001	01-Jul-04	ROUNDUP ORIGINAL HERBICIDE	00052400445		CA	HC	Unknown Adult (18-64 years old) Female spilled a bottle in the back of her car. She rinsed the seats off with a hose and then squeezed the water out of the sham with her hands. She reported Numb Fingertips.
015498	001	01-Jul-04	ROUNDUP W & G KILLER READY TO USE	07199500023		OH	HC	Unknown Adult (18-64 years old) Male sprayed some weeds along his driveway with the product. The wind blew some of the product back on his Leg. He reported Blisters on Legs.

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015499	001	01-Jul-04	ROUNDUP	00052400445		LA	HC	Unknown Adult (18-64 years old) Male sprayed the product and the hose came loose. Some of the product got on his hands. He reported Blisters, Swelling, Pain.
015501	001	01-Jul-04	ROUNDUP RTU W & G KILLER1	07199500023		NY	HC	Unknown Adult (18-64 years old) Male sprayed the formulation product. He reported Dermal Irritation/Pain.
015502	001	01-Jul-04	ROUNDUP RTU POISON IVY & TOUGH BRUSH KILLER	07199500032		OH	HC	A man reported Back Pain, Throat Pain, and Chest Pain after he applied the product on a windy day.
015505	001	01-Jul-04	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		NC	HC	Unknown Adult (18-64 years old) Female reported Fluid-filled Blisters on Legs, Rash after the product was spilled.
015483	071	29-Aug-04	BASIC SOLUTIONS WEED AND GRASS KILLER	07199500027 000239	COLORADO SPRINGS	CO	HC	A 11 year old Child reported Hives/Welts all over her body while her mother treated their lawn with the product.
015483	079	16-Aug-04	GROUND CLEAR COMPLETE VEGITATION KILLER CONCENTRATE	00023902657	IRVING	TX	HC	Unknown Adult (18-64 years old) Male reported Hives, Itchy Rash, and Swollen Lower Lip.
015535	001	18-Aug-04	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500017		TX	HC	Unknown Adult (18-64 years old) Male used the product off and on for six years. He applied the product on a windy day and reported Shortness of Breath.
015541	001	01-Aug-04	ROUNDUP W & G KILLER SUPER CONCENTRATE	07199500018		CA	HC	Unknown Adult (18-64 years old) Male used the product about 2 weeks ago. He reported Swollen Eyes.

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015544	001	01-Aug-04	ROUNDUP HERBICIDE	00052400445		MI	HC	Unknown Adult (18-64 years old) Female applied the product using a pressure sprayer. The hose came loose and the left side of her Face and Body was splashed with the product. She reported Coughing, Bronchitis.
015545	001	01-Aug-04	ROUNDUP HERBICIDE	00052400445		FL	HC	Unknown Adult (18-64 years old) Female used the diluted product about one month ago. She opened the sprayer and no liquid was released, but is concerned with the air that was released from the sprayer. She reported Congestion later that evening. She was Diagnosed with Chronic Sinusitis.
015561	001	09-Sep-04	ROUNDUP PRO	00052400445		OR	HC	Unknown Adult (18-64 years old) Male used the product about one month ago. He may have splashed himself in the face with a drop of the product. He reported Edema, Fever, and Salivary Gland Swelling.
015562	001	27-Sep-04	ROUNDUP ORIGINAL HERBICIDE	00052400445		TX	HC	Unknown Adult (18-64 years old) Male sprayed the diluted product from his tractor. He reported Joint Pain.
015563	001	09-Sep-04	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		NY	HC	Unknown Adult (18-64 years old) Male pulled some weeds in the garden where his wife sprayed the product the previous day. He reported Red Itchy Rash, Blisters

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015565	001	13-Sep-04	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		HI	HC	Unknown Adult (18-64 years old) Male sprayed the diluted product 10 days ago when it was windy. He reported Fatigue, Loss of Appetite.
015567	001	01-Sep-04	ROUNDUP READY TO USE W & G KILLER	07199500008		KS	HC	Unknown Adult (18-64 years old) Male used diluted product and got a small amount on his hands. He reported Tiny Lesions on his Hands, Swollen Fingers.
015568	001	09-Jan-04	ROUNDUP POISON IVY AND TOUGH BRUSH KILLER2 READY TO USE	07199500032		AL	HC	Unknown Adult (18-64 years old) Female sprayed the diluted product. She reported Coughing/Choking, Bronchitis
015569	001	01-Sep-04	ROUNDUP POISON IVY AND TOUGH BRUSH KILLER2 READY TO USE	07199500032		AL	HC	Unknown Adult (18-64 years old) Female mowed the grass and afterward she sprayed it with the diluted product. She wore shorts and reported Red and Swollen Skin, Blisters, Irritation/Pain.
015602	055	29-Sep-04	GROUND CLEAR COMPLETE VEGETATION KILLER CONCENTRATE	00023902657	CANAL FULTON	OH	HC	Unknown Adult (18-64 years old) Male used product 10 days ago when it was windy. Some of the product blew in his face that he wiped with his hands. He reported Blisters on Face.
015724	001	01-Oct-04	BUCCANEER	00052400445		MT	HC	Unknown Adult (18-64 years old) Male sprayed product. He pulled weeds that pierced his finger leaving a long cut. He reported Redness and Swollen Hand, Wrist.

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015766 001	11-Oct-04	ROUNDUP WEED AND GRASS KILLER READY TO USE	07199500032		CA	HC	Unknown Adult (18-64 years old) Female reported sprayed the product and got some on her hands. She rubbed her eyes and reported Ocular Irritation/Pain.
015792 001	01-Nov-04	ROUNDUP CONCENTRATE WEED & GRASS KILLER	07199500017		FL	HC	Unknown Adult (18-64 years old) Male used the diluted product. He wore shorts during the application and thinks he might have gotten some of the mist of the product on his legs. He reported Redness of Skin, Irritation, and Blisters.
015718 001	01-Oct-04	ROUNDUP READY TO USE WEED & GRASS KILLER	07199500026		FL	HC	Unknown Adult (18-64 years old) Male mixed the product and some of it got on his fingers. He rinsed his hands with water, but he may have rubbed his eyelids with his hand. He reported Swollen Face, Itchy Eyelids.
015784 009	15-Sep-04	ORTHO BASIC SOLUTIONS WEED & GRASS KILLER CONCENTRATE	07199500006 000239	PORTLAND	OR	HC	A 45 year old Male reported Rash, Pruritus after he sprayed the product that splashed on his hands.
015823 001	04-Dec-04	ROUNDUP READY TO USE WEED AND GRASS KILLER	07199500008		AZ	HC	The nozzle on the sprayer dripped some of the product on a man's hands. An Unknown Adult (18-64 years old) Male reported Blisters.
015903 004	17-Nov-04	BASIC SOLUTIONS WEED AND GRASS KILLER	07199500027 000239	HOMESTEAD	FL	HC	A 66 year old Male applied product and reported Skin Peeling.

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015976	001	01-Jan-05	ROUNDUP READY TO USE POISON IVY & TOUGH BRUSH KILLER	07199500032		AZ	HC	Unknown Adult (18-64 years old) Male used the diluted product and did not wear any type of protective clothing at the time. Some of the product may have gotten some onto his skin. He reported Slurred Speech, Muscle Incoordination, Diarrhea, and Difficulty Concentrating.
015987	001	06-Jan-04	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		NC	HC	Unknown Adult (18-64 years old) Female treated crabgrass with the product on a windy day. She reported Ocular Irritation, Rash.
015974	007	22-Jan-05	BASIC SOLUTIONS WEED AND GRASS KILLER	07199500027 000239		TX	HC	Unknown Adult (18-64 years old) Female touched the neck of the product bottle and later rubbed the corner of her Eye. She reported Bloody Spot on Sclera.
016117	002	01-Mar-05	ROUNDUP HERBICIDE	00052400445		CA	HC	Unknown Adult (18-64 years old) Female sprayed the product and reported Slurred Speech.
016117	004	01-Mar-05	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		SC	HC	Unknown Adult (18-64 years old) Male reported Rash after some of the product spilled on his hand.
016117	005	01-Mar-05	ROUNDUP CONCENTRATE WEED & GRASS KILLER	07199500017		CA	HC	A man applied the product with a pump that was under pressure. Some of the product splashed into his eyes and on his Face. Unknown Adult (18-64 years old) Male reported Eye Irritation, Redness.

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016117	006	01-Mar-05	ROUNDUP CONCENTRATE WEED & GRASS KILLER	07199500017		FL	HC	The woman initially had shoes on when the product was sprayed on the grass. She ran back and forth into and out of her house. Unknown Adult (18-64 years old) Female reported Burning Sensation, Lesions on her Feet, Pain.
016126	012	12-Mar-05	ORTHO BASIC SOLUTIONS WEED & GRASS KILLER CONCENTRATE	07199500006 000239		AZ	HC	A 52 year old Female reported a Chest Pain after she applied the product for about 5 hours.
016218	001	19-Apr-05	ROUNDUP WEED & GRASS KILLER1 SUPER CONCENTRATE	07199500018		CA	HC	Unknown Adult (18-64 years old) Male got some of the product on his hands as the bottle was leaking. He reported Peeling Hands, Burning Sensation On Skin, and Low Platelet Count.
016218	004	01-Apr-05	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		MO	HC	Unknown Adult (18-64 years old) Male diluted product and sprayed dandelions for four hours. He reported Chest Pain, Nausea, Chills, and Diarrhea.
016218	005	01-Apr-05	ROUNDUP ULTRAMAX	00052400512		TN	HC	Unknown Adult (18-64 years old) Female reported Ocular Irritation/Pain, Redness, and Corneal Abrasions. She was at the golf course while they sprayed the product with a sprayer for weeds. The person carrying the sprayer accidentally triggered the spray directly into the woman's Face, Eyes, and on her Skin

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016218 006	01-Apr-05	ROUNDUP	00052400445		VA	HC	Unknown Adult (18-64 years old) Male spilled the diluted product on his hands that he did not immediately wash. He reported Burning Sensation, Skin Peeling, and Redness.
016247 013	24-Apr-05	POWER FORCE GRASS & WEED KILLER 1 GAL READY-TO-USE	06776000061 072155	LAS VEGAS	NV	HC	Unknown Adult (18-64 years old) Female reported Rash on her Skin. Some of the product splashed on her skin and she didn't rinse it off.
016316 001	01-May-05	ROUNDUP W & G KILLER READY TO USE PLUS	07199500033		NC	HC	Unknown Adult (18-64 years old) Male applied the product on a windy day. He reported Pruritus, Rash.
016316 002	01-May-05	ROUNDUP POISON IVY & TOUGH BRUSH KILLER2 READY TO USE	07199500032		OR	HC	Unknown Adult (18-64 years old) Male used the product for about 15 minutes and reported Lung Secretions.
016316 003	01-May-05	ROUNDUP POISON IVY & TOUGH BRUSH KILLER2 READY TO USE	07199500032		MA	HC	Unknown Adult (18-64 years old) Male reported Lump behind his Ear, Sensitivity to Touch.
016316 007	01-May-05	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		SC	HC	Unknown Adult (18-64 years old) Female mixed one capful of the product in her sprayer. The sprayer became clogged that she removed and some of the product got onto her skin of her Arms. She reported Weakness.
016316 008	01-May-05	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		CA	HC	Unknown Male Child ( 4-16 years old) had some of the product splashed in his left eye when he took the lid off a pressurized

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							sprayer. He reported Burning Eyes, Irritation.
016318	001	18-Apr-05	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE		OH	HC	Unknown Adult (18-64 years old) Female used the product and got some of the product on her left hand. She reported Irritation, Redness, and Skin Peeling.
016318	002	11-May-05	ROUNDUP WEED & GRASS KILLER 1 SUPER CONCENTRATE		TN	HC	Unknown Adult (18-64 years old) Female used the diluted product and accidentally stepped into a hole and inadvertently sprayed herself in the Face. She reported Coughing, Chest Pain, Aching, and Thick Mucous from Nose.
016318	003	18-Apr-05	ROUNDUP WEED & GRASS KILLER READY TO USE		NM	HC	Unknown Adult (18-64 years old) Female reported Redness, Swollen, Eyelid is Peeling. The woman's son sprayed the weeds with the product several days earlier.
016318	009	14-May-05	NUFARM AQUANEAT AQUATIC HERBICIDE		GA	HC	A truck carrying a diluted product parked behind a restaurant. An Adult (18-64 years old) Male reported Stomach Pain, Vomiting, and Shortness of Breath.
016352	239	11-May-05	SEASON-LONG GRASS & WEED KILLER 32OZ	MISSION VIEJO	CA	HC	Unknown Adult (18-64 years old) Male used the product in the morning and reported Nausea, Vomiting, Dizziness/Vertigo.

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016440	001	09-Jun-05	GLYFOS X-TRA HERBICIDE	00478700023		KY	HC	Unknown Adult (18-64 years old) Female applied the product and reported Swollen Throat, Edema.
016496	001	01-Jun-05	ROUNDUP ULTRA	00052400475		IL	HC	Unknown Adult (18-64 years old) Male sprayed the product and the wind blew it in his face. He reported Blisters, Itching, and Red Spots.
016499	001	18-Jun-05	ROUNDUP HERBICIDE	00052400445		OH	HC	A 74 year old Male reported Fever, Coughing, Blood in Stool, after a neighbor sprayed the product in his field.
016500	001	01-Jun-05	ROUNDUP ULTRAMAX	00052400512		CA	HC	Unknown Adult (18-64 years old) Male sprayed the diluted product in his yard. He reported Difficulty Breathing and was hospitalized.
016504	001	01-Jun-05	ROUNDUP ORIGINAL	00052400445			HC	Unknown Adult (18-64 years old) Male applied the product and reported Itching, Nausea, Vomiting, Chest Pain, Shortness of Breath.
016506	001	20-Jun-05	ROUNDUP ORIGINAL	00052400445		NC	HC	Unknown Adult (18-64 years old) Male reported Rash on Hand, Lungs, Clogged Sinuses, and Burning Eyes.
016508	001	01-Jun-05	ROUNDUP ULTRA	00052400475		IN	HC	Unknown Adult (18-64 years old) Male sprayed the diluted product for one hour. He got a small amount on his clothes. He reported Dizziness, Ataxia, and Numbness.
016509	001	29-Jun-05	ROUNDUP HERBICIDE	00052400445		MS	HC	Unknown Adult (18-64 years old) Male reported Chest Pain and Nausea after spraying the product.

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016512 001	01-May-05	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		TN	HC	A 16 year old Male reported Dizziness, Chest Pain, and Nausea after using the product on some weeds.
016513 001	29-May-05	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023		MT	HC	A 45 year old Female used the product on multiple areas of her yard while she wore sandals and capri pants. She reported Itching, Redness, Rash.
016514 001	01-Jun-05	ROUNDUP READY-TO-USE POISON IVY & TOUGH BRUSH KILLER PLUS	07199500036		TX	HC	Unknown Adult (18-64 years old) Male cut back bamboo and sprayed the stumps with the diluted product. He reported Dizziness, Sweating, and Weakness.
016522 001	16-Jun-05	ROUNDUP WEED AND GRASS KILLER READY TO USE	07199500008		NY	HC	Unknown Adult (18-64 years old) Female purchased a bottle of the product and left it on the floor of her vehicle. The bottle spilled on the floor of her vehicle. She reported Dizziness, Shortness of Breath, Chest Pain, and Tingling.
016523 001	01-Apr-05	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		CA	HC	Unknown Adult (18-64 years old) Male used diluted product. The sprayer leaked onto his hands he was spraying it. He reported Skin Pain.
016530 161	07-Jul-05	SEASON-LONG GRASS & WEED KILLER 32OZ	00023902516	PORTLAND	OR	HC	Unknown Adult (18-64 years old) Female reported Swelling, Redness, and Bumps.
016542 001	17-Jun-05	ROUNDUP L & G READY-TO-USE GRASS & WEED KILLER	07199500008		PA	HC	A woman sprayed the product in the cracks of the bricks around her pool. The woman's children

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								reported Blisters on Feet.
016543	001	24-Jun-05	ROUNDUP W & G KILLER CONCENTRATE	07199500017		MT	HC	Unknown Adult (18-64 years old) Male sprayed the product which splashed on his face and skin. He reported Shortness of Breath.
016546	001	12-Jun-05	ROUNDUP READY-TO-USE POISON IVY & TOUGH BRUSH KILLER PLUS	07199500036		MS	HC	Unknown Adult (-18-64 years old) Female reported Earache, Oral and Ocular Burning after inhaling the product.
016547	001	24-Jun-05	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500017		MT	HC	Unknown Adult (18-64 years old) Male sprayed the product that splashed on his Face. He reported Fatigue, Dyspnea.
016589	001	02-Jul-05	GLYFOS X-TRA HERBICIDE	00478700023		TX	HC	A 75 year old Male's gloves and pants were soaked with the product due to a leak in the sprayer hose. He reported Blurred Vision, Itching, Burning Rash, Dizziness, and Confusion.
016681	001	01-Jul-05	ROUNDUP HERBICIDE	00052400445		MO	HC	Unknown Adult (18-64 years old) Male sprayed the product using a backpack sprayer and some of the product leaked onto his skin. He reported Lung Congestion.
016681	003	01-Jul-05	ROUNDUP READY TO USE W & G KILLER1	07199500023		AR	HC	Unknown Adult (18-64 years old) Female sprayed the product on a windy day. She reported Shortness of Breath, Blisters in her Mouth and Lips.

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
016681	004	01-Jul-05	ROUNDUP READY-TO-USE W & G KILLER1	07199500023		CA	HC	A 6 year old Male Child played nearby while his Mother sprayed the product on a windy day. The Mother reported Dizziness, Nausea and her Child Collapsed and had a Seizure.
016681	005	01-Jul-05	ROUNDUP READY-TO-USE W & G KILLER1	07199500023		TX	HC	Unknown Adult (18-64 years old) Female stated that her friend sprayed the product 2 weeks ago on a driveway. She reported Rash, Blisters, and Swollen Hand.
16681	007	01-Jul-05	ROUNDUP W & G KILLER READY TO USE	07199500032		ID	HC	Unknown Adult (18-64 years old) Male used the product and got it on his hands. He later ate cake with his fingers and drank some water. He reported Chest Pain, Stomach Ache, and Shortness of Breath.
016681	008	01-Jul-05	ROUNDUP W & G KILLER READY TO USE	07199500032		GA	HC	Unknown Adult (18-64 years old) Male sprayed the product while wearing shorts on a windy day. He reported Rash on his Ankle, Stomach Pain, and Chest Pain.
016707	001	30-Jul-05	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		OH	HC	Unknown Adult (18-64 years old) Male spent almost all day spraying a large area at home with the diluted product. He used a hand held sprayer to fill and refill the container many times. He reported Slight Swelling, Throat Pain, and Tightness in his Neck.

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
016707	002	15-Jun-05	ROUNDUP EXTENDED CONTROL WEED & GRASS KILLER 1 PLUS WEED PREVENTER	07199500021		NC	HC	Unknown Adult (18-64 years old) Female used the product and reported Malaise, Rash, Shortness of Breath, Nausea.
016707	004	17-Aug-05	ROUNDUP W & G KILLER1 SUPER CONCENTRATE	07199500018		AL	HC	Unknown Adult (18-64 years old) Male used the diluted product according to the package directions. He may have gotten some of the product on his skin. He reported Rash, Muscle Weakness, and Irritation.
016707	006	11-Aug-05	ROUNDUP HERBICIDE	00052400445		OR	HC	Unknown Adult (18-64 years old) Female sprayed the product in an orchard. She reported Malaise, Bloody Diarrhea, Abdominal Cramps, Achy Muscles and Chills.
016707	007	15-Jun-05	ROUNDUP PRO	00052400512		CA	HC	Unknown Adult (18-64 years old) Male sprayed a field. He reported Respiratory Problems, Pneumonia.
016707	009	22-Jul-05	MIRAGE	00052400445		AR	HC	Unknown Adult (18-64 years old) Female reported Itching, Redness, and Swollen Eyes after the product was applied.
016707	011	15-Aug-05	ROUNDUP CONCENTRATE W & G KILLER	07199500017		CA	HC	Unknown Adult (18-64 years old) Female sprayed the diluted product. She reported Itching, Redness, and Burning Sensation.
016738	004	23-Aug-05	ACCORD XRT HERBICIDE	06271900517	MONTGOMERY	LA	HC	A 50 year old Male, who did not wear glasses, reported spraying the product for several hours. Did have mask on but not safety glasses. During the spraying some

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
								of the mist got on his face. He reported Testicular Pain, Nausea.
016784	001	09-Sep-05	ROUNDUP READY TO USE W & G KILLER1	07199500023		SC	HC	Unknown Adult (18-64 years old) Female was getting ready to spray the product and the handle broke off. The liquid spilled and she reported Ocular Irritation, Blurred Vision.
016786	001	29-Sep-05	ROUNDUP W & G KILLER SUPER CONCENTRATE	07199500025		MT	HC	Unknown Adult (18-64 years old) Male sprayed diluted product on a windy day. He reported Blisters on his Arms, Redness, and Burning Sensation.
016787	001	30-Sep-05	ROUNDUP W & G KILLER1 SUPER CONCENTRATE	07199500018		MS	HC	Unknown Adult (18-64 years old) Male applied the product and some of the spray blew in his face. He reported Sore Throat, Chest Pain.
016806	001	06-Sep-05	ROUNDUP WEED AND GRASS KILLER READY TO USE FROM MONSANTO	07199500008		FL	HC	Unknown Adult (18-64 years old) Female sprayed the diluted product around the house and fence line on a windy day. She reported Hives.
016805	001	01-Jan-05	ROUNDUP WEED & GRASS KILLER CONCENTRATE	07199500026		KY	HC	Unknown Adult (18-64 years old) Female poured product from the bottle into a sprayer and it splashed on her hands. She reported Ocular Irritation, Burning Eyes, and Redness.

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
016848	001	15-Aug-05	GLYFOS X-TRA HERBICIDE	00478700023		ID	HC	Unknown Adult (18-64 years old) Male used the product on a Farm intermittently for the past (2) months. He reported Joint Pain.
016879	003	01-Jul-05	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023		OH	HC	Unknown Adult (18-64 years old) Male got some of the product on his fingers and thumb. He washed off the area with soap and water. He reported Rash.
016879	004	01-Oct-05	ROUNDUP HERBICIDE	00052400445		MI	HC	A 68 year old Male held a container of the product that leaked on his left hand. He reported Memory Loss, Blisters.
016879	005	01-Aug-05	GLY 4 PLUS	00052400454 072693		GA	HC	Unknown Adult (18-64 years old) Male applied the product. He wore protective clothing and showered after applying the product. He reported Blurred Vision, Dizziness.
016879	006	01-Oct-05	ROUNDUP W & G KILLER READY TO USE	07199500032		IA	HC	A Grandmother applied the product in her yard. She later allowed her grandson to play in the yard with a hose. The product may have gotten onto the child's skin. The grandson reported Fever, Vomiting
016879	008	01-Oct-05	BUCCANEER PLUS	00052400454		KY	HC	Unknown Adult (18-64 years old) Male applied the product and reported Nausea, Vomiting, Dizziness.
016882	001	01-Nov-05	GLYSTAR PLUS	04275000061	PEORIA	AZ	HC	The product was applied at a trailer park and a Child (3-8 years old) Played nearby. The Child reported Convulsions, Fever.

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**Chemical: Glyphosate****103601****Human Incidents**

Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
016986 001	01-Aug-05	GLY 4 PLUS	00052400454 072693		AL	HC	Unknown Adult (18-64 years old) Male sprayed the product while wearing a dust mask. He reported a Chest Cold.
017078 001	01-Jun-05	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500023		IN	HC	Unknown Adult (18-64 years old) Female used the product and reported Itchy Hands.
017263 001	01-Aug-05	ROUNDUP	00052400445		KS	HC	A park representative sprayed the sand for sand mites with the product. A Female Child (3-8 years old) walked across the sand at the local park. She reported Chemical Burn, Blisters, Bacterial Infection.
017391 012	13-Apr-06	BASIC SOLUTIONS WEED AND GRASS KILLER	07199500027 000239		CA	HC	Unknown Adult (18-64 years old) Female used the product and reported Vomiting, Diarrhea.
017403 001	01-Apr-06	ROUNDUP W & G KILLER READY TO USE	07199500008		NC	HC	A 36 year old Male sprayed the product and reported Numbness, Tingling, Blurred Vision.
017403 005	27-Apr-06	ROUNDUP W & G KILLER READY-TO-USE	07199500033		AL	HC	Unknown Adult (18-64 years old) Female sprayed the product for thirty minutes and reported Malaise.
017403 006	01-Feb-06	ROUNDUP W & G KILLER READY TO USE	07199500032		NE	HC	Unknown Adult (18-64 years old) Male sprayed product on a windy day. He reported Rash on his Stomach, Arms and Legs.
017500 010	03-May-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516		CA	HC	Used product two days ago, and a 62 year old Female reported Headache, Painful Neck, Photophobia, Oral Irritation,

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Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description	
							Vomiting	
017500	019	07-May-06	BASIC SOLUTIONS WEED AND GRASS KILLER	07199500027 000239	BROWNSVILLE	TX	HC	Unknown Adult (18-64 years old) Female used the product says that got on her hands. She reported Rash on Arms and Legs.
017500	045	23-May-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516	NEWBERG	NY	HC	A 86 year old Female reported Erythema/Flushed, Rash, Swollen Face after pulling weeds in her yard that was applied the day before.
017500	049	24-May-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516		OH	HC	Unknown Adult (18-64 years old) Female sprayed product. She reported Dermal Irritation/Pain, Rash, and Pruritus.
017538	001	21-May-06	SHOOTOUT WEED & GRASS KILLER 2	06776000048 009688	HENDERSON	TN	HC	A 28 year old Male used the product and experienced Bradycardia, Dizziness, Numbness.
017585	008	23-May-06	DURANGO HERBICIDE	06271900324	WAUSEON	OH	HC	Unknown Adult (18-64 years old) Male, who is a farmer, reported Skin Rash after he applied the product.
017620	036	14-Jun-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516		CA	HC	A 61 year old Female reported Swelling Eyes after using the product in her yard yesterday.
017620	063	21-Jun-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516	WICHITA	KS	HC	A 4 year old Male Child was playing with a spray bottle. The child reported Hives on his Chest and Face.

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017620	071	23-Jun-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516		NY	HC	Unknown Adult (18-64 years old) Female sprayed the product for about an hour yesterday. She reported Vomiting, Belching, and Chest Pain.
017620	072	24-Jun-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516		NJ	HC	Unknown Adult (18-64 years old) Male was sitting in a small room and fell asleep in a chair with the product that was leaking out of the bottle and onto the carpet. He reported Confusion.
017620	401	17-Jun-06	SEASON-LONG GRASS & WEED KILLER 32OZ READY-TO-USE	00023902516	PLEASANT GARDEN	NC	HC	Unknown Adult (18-64 years old) Female sprayed the product that got on her legs. She reported Blisters on her Legs.
017664	001	20-Jun-06	GLYFOS	00478700031	MANNING	SC	HC	Unknown Adult (18-64 years old) Male reported Eye Irritation. A tractor was struck by another vehicle and a tank ruptured. The man's body was drenched and the product got in his eyes.
017747	027	09-Jul-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516	BENJI	CA	HC	Unknown Adult (18-64 years old) Male, who smoked while he the applied product on a windy day. He reported Vomiting, Diarrhea, Congestion, Coughing/Choking, Nausea, and Throat Irritation.
017797	001	24-May-06	ROUNDUP WEED & GRASS KILLER READY-TO-USE PLUS	07199500033		GA	HC	Unknown Adult (18-64 years old) Female got some of the product in her eyes while she applied it. She reported Ocular Irritation, Painful Eyelids.

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017798 001	15-May-06	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		MI	HC	Unknown Adult (18-64 years old) Male applied the product and felt the product blow in one of his eyes. He did not flush the eye immediately. The man reported Burning Sensation in one Eye, Swollen Eyelid.
017800 001	30-Apr-06	ROUNDUP PRO	00052400475		OH	HC	Unknown Adult (18-64 years old) Male used the product at his workplace. He reported Hives/Welts all over his body, Inflamed Feet, Sweating, and Severe Itching.
017801 001	30-May-06	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023		AL	HC	Unknown Adult (18-64 years old) Female was discarding a container of the product and some splashed into her eyes. She reported Eye Irritation, Redness, and Corneal Abrasion.
017802 001	10-May-06	ROUNDUP	00052400445		ID	HC	A 70 year old Male accidentally sprayed himself in the eyes with the product. He reported Ocular Irritation, Corneal Abrasion.
017804 001	26-May-06	ROUNDUP	00052400445		PR	HC	Unknown Adult (18-64 years old) Female did not wear any protective clothing. The woman poured the packet into a gallon bucket and used her hands to grab water out of bucket and splash it on the weeds. She did not go inside and wash her hands. She reported Rash, Blisters, Pruritus, and Redness.

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Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
017805 001	02-May-06	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		KY	HC	Unknown Adult (18-64 years old) Female spilled some of the product on her hands while transferring it to the sprayer. She states she had several minor cuts on her hands that were several days old and this product may have gotten into these cuts. She reported Abdominal Cramping, Diarrhea, and Blood in Stool.
017809 004	23-May-06	RASCAL PLUS	00052400454		OH	HC	Unknown Adult (18-64 years old) Male used the product that got under his rubber glove that he was used. He reported Blisters, Rash.
017809 007	18-Jun-06	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		IA	HC	Unknown Adult (18-64 years old) Female was exposed after some of the product splashed into one of her eyes. She splashed some water into her eye at the time of the exposure. She reported Burning Sensation, Eye Irritation, and Redness.
017809 008	06-Jun-06	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		PA	HC	Unknown Adult (18-64 years old) Female used the product and accidentally sprayed a little into her eye. She reported Burning and Painful Eyes.
017809 009	04-Jun-06	ROUNDUP READY-TO-USE EXTENDED CONTROL WEED & GRASS KILLER PLUS WEED PR	00024100425 071995		OK	HC	Unknown Adult (18-64 years old) Male sprayed the diluted product and some of it blew back on his legs. He reported Numbness.

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Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
017828 001	07-Jul-06	ROUNDUP READY-TO-USE POISON IVY & TOUGH BRUSH KILLER PLUS	07199500036		SC	HC	Unknown Adult (18-64 years old) Female used the product for 45 minutes. She reported Dehydration, Diarrhea.
017829 001	08-Jul-06	ROUNDUP CONCENTRATE WEED & GRASS KILLER1	07199500017		VA	HC	Unknown Adult (18-64 years old) Female mixed the product and as she unscrewed the top of the pressurized sprayer she inhaled some of the fumes. She reported Coughing.
017857 001	07-Aug-06	GLYFOS	00478700031	CEDAR CITY	UT	HC	A 75 year old Male was accidentally exposed to product when a hose ruptured due to a clogged line. The product splashed into his face. He reported Vomiting, Bloating, Nausea, Lethargy, Hematemesis.
017863 055	11-Jul-06	ORTHO SEASON LONG GRASS & WEED KILLER PULL N SPRAY RTU	00023902516	GREAT FALLS	MT	HC	Unknown Adult (18-64 years old) Female reported Blisters, Pruritus, Erythema, and Skin Peeling. She applied the product outside and some of the liquid splashed on her skin and her foot.
017967 001	07-Jul-06	ROUNDUP	00052400445		LA	HC	A woman's son sprayed all over her greenhouse. The grass/weeds were at least one foot high in the area. The woman was in the area while he was sprayed the product. She walked and worked in the area for quite sometime while she wore her shoes and socks. The woman reported Redness, Swelling.

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
017970	001	14-Sep-06	ROUNDUP WEED & GRASS KILLER READY-TO-USE PLUS	07199500033		AZ	HC	Unknown Adult (18-64 years old) Male applied the product and some of it got on his hands. He did not immediately wash his hands. He reported Shortness of Breath, Chest Pain, and Anxiety.
017972	001	01-Jun-06	RODEO	00052400343		OH	HC	Unknown Adult (18-64 years old) Male applied the product. He reported a Headache and other symptoms at the time. Two months later he reported Low Blood Counts.
017974	001	01-Aug-06	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		NY	HC	Unknown Adult (18-64 years old) Female sprayed the product for about 15 minutes around her patio with flip flops on. She reported Burning Sensation, Pruritus, Blisters, and Redness.
018011	001	28-May-06	ROUNDUP CONCENTRATE WEED & GRASS KILLER1	07199500017		CA	HC	Unknown Adult (18-64 years old) Male sprayed the product. When he finished spraying he washed his hands immediately. Several days later, he reported Red Spots on Both Hands.

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
018012	001	01-Sep-06	ROUNDUP CONCENTRATE WEED & GRASS KILLER1	07199500017		VT	HB	Unknown Adult (18-64 years old) Male owns a small Christmas tree farm. He sprayed the product using a backpack sprayer around the trees and down the rows. He wore rubber boots when spraying and does not remember the actual spraying being eventful or what he thought to be dangerous. At the time of the call to the PCC he stated that he was sick for the past several weeks. He was very active and worked a lot prior to becoming ill. The man reported Lightheadedness any time he stands up. He has also been very sick to his stomach. PCC discussed the product toxicity and advised the symptoms are not consistent with appropriate use of the containing product.
018013	001	29-Oct-06	ROUNDUP READY-TO-USE WEED & GRASS KILLER	07199500008		CA	HC	Unknown Adult (18-64 years old) Female was working in her yard using the product. About an hour after she finished applying the product she reported Eye Irritation, Redness.
018364	011	23-Feb-07	BASIC SOLUTIONS WEED AND GRASS KILLER	07199500027 000239		FL	HC	Unknown Adult (18-64 years old) Female sprayed the product in her yard. The woman reported Dermal Irritation, Bullae/Blisters, and Erythema.

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Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
018485	001	01-Apr-07	ROUNDUP READY-TO-USE WEED & GRASS KILLER	07199500008		PA	HC	Unknown Adult (18-64 years old) Male used the product (2) days ago. He does not remember any direct contact with the product to skin or by mist. He reported Rash, Redness, Pruritus, and Numbness. The PCC discussed the product Toxicity and advised the symptoms are unrelated. Recommend to continue follow up with their Physician.
018486	001	05-Apr-07	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023		MO	HC	A 60 year old Male reported Bradycardia and Hypotension after product use.
018489	001	15-Apr-07	ROUNDUP CONCENTRATE WEED & GRASS KILLER1	07199500017		WI	HC	Unknown Adult (18-64 years old) Male applied the product with a metal sprayer and a mist came out of it. He reported Chest Congestion, Difficulty Breathing.
018490	001	24-Apr-07	ROUNDUP READY-TO-USE EXTENDED CONTROL WEED & GRASS KILLER PLUS WEED PR	00024100425 071995		MT	HC	Unknown Adult (18-64 years old) Female used the product and the nozzle would not work so she changed it. The product splashed in her face and hair and in her right eye. She reported Swollen Eyelid, Ocular Irritation.
018492	001	30-Apr-07	ROUNDUP READY-TO-USE WEED & GRASS KILLER	07199500008		IL	HC	Unknown Adult (18-64 years old) Female reached for the bottle of the product in her garage. The cap was loose on the container and some of it splashed in herFace, Mouth, Eyes. She reported Eye Irritation, Eye Burning, and Eye

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Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
							Infection.
018494	001	16-Apr-07	ROUNDUP		FL	HC	Unknown Adult (18-64 years old) Male played golf at a course and reported Weakness and Dizziness. The product was previously applied to the course.
018599	068	28-May-07	KGRO GRASS & WEED KILLER (READY-TO-USE)		OR	HC	Husband sprayed product while he wore shorts and sandals. He reported Diarrhea, Vomiting.
018631	001	27-May-07	ROUNDUP		MO	HC	Unknown Adult (18-64 years old) Male who is a farmer applied the product. He reported Chest Pain, Difficulty Breathing.
018632	001	26-Apr-07	ROUNDUP READY-TO-USE EXTENDED CONTROL WEED & GRASS KILLER1 PLUS WEED P		NC	HC	Unknown Adult (18-64 years old) Male sprayed diluted product with some unprotected areas on his legs. He reported Redness, Swollen.
018634	001	06-May-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE PLUS		ID	HC	Unknown Adult (18-64 years old) Female sprayed the product on a windy day. She reported Swollen Eyelids, Eye Infection.
018635	001	10-May-07	ROUNDUP READY-TO-USE EXTENDED CONTROL WEED & GRASS KILLER1 PLUS WEED P		SC	HC	Unknown Adult (18-64 years old) Male used the product that splashed in his Face from the nozzle. He reported Ocular Irritation.

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018639 001	29-May-07	ROUNDUP READY-TO-USE WEED & GRASS KILLER	07199500008		FL	HC	Unknown Adult (18-64 years old) Male sprayed the product 3-4 days ago and it had turned the plants yellow. About one hour ago he was pulling the weeds and he got distracted and rubbed his eyes with his hands prior to washing them. He reported Redness, Eye Irritation.
018640 001	01-Jul-06	ROUNDUP	00052400445		GA	HC	Unknown Adult (18-64 years old) Male reported Redness, Eye Irritation. Some of the product blew in his eyes on a windy day.
018718 005	13-Jun-07	POWER FORCE GRASS & WEED KILLER 1 GAL RTU	06776000061 072155	ELGIN	IL	HC	A 64 year old Female reported Pruritus, Rash. She wiped her husband's boots off after he wore them to while he applied the product.
018726 001	26-May-07	GLYPHOSATE CONCENTRATE	00478700035	OXFORD	NC	HC	Unknown Adult (18-64 years old) Male applied the product and reported Rash, Fever, Joint Pain, Joint Swelling.
018732 046	10-Jun-07	KGRO GRASS & WEED KILLER 1 (READY-TO-USE)	07199500027 073327		CA	HC	Unknown Adult (18-64 years old) Male used the product on his lawn and did not wear gloves. He reported Dermal Irritation, Erythema, and Edema.
018767 006	18-Jun-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500033		GA	HC	Unknown Female Child (4-10 years old) sprayed herself in the eyes with the product. She reported Ocular Irritation, Eye Swollen, and Redness.

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**Chemical: Glyphosate****103601****Human Incidents**

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
018767	007	10-Jun-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		MI	HC	Unknown Adult (18-64 years old) Female used the product at home and got the product on both of her feet and part of her legs. She reported Itching, Redness, and Swelling.
018767	008	25-Jun-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		KY	HC	A 52 year old Male reported Facial Edema and was treated at a hospital. The patient worked for about (4) hours with the product.
018767	009	13-Jun-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		IN	HC	Unknown Adult (18-64 years old) Female spilled some of the product on her foot. She reported Rash, Peeling Skin.
018767	010	04-Jun-07	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	07199500025		MD	HC	Unknown Adult (18-64 years old) Male got some of the product in both of his Eyes when he mixed the product. He reported Ocular Irritation, Blurred Vision, and Corneal Abrasion.
018818	008	19-Jun-07	ORTHO TOTAL KILL WEED & GARDEN KILLER CONCENTRATE HERBICIDE	07199500007 000239	ALBUQUERQUE	NM	HC	Unknown Adult (18-64 years old) Male reported that his neighbor spilled the product near their air conditioner. He reported Coughing, Respiratory Irritation, Headache, Chest Tightness, and Wheezing.
018818	023	08-Jul-07	ORTHO TOTAL KILL WEED & GARDEN KILLER CONCENTRATE HERBICIDE	07199500007 000239		TX	HC	Unknown Adult (18-64 years old) Male used the product for about 4 hours. He used a mask and goggles when he applied the product on a hot day. He reported Redness, Swollen Eye.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

## IDS Report

3/12/09

Chemical: Glyphosate

103601

Human Incidents

Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
018818 076	16-Jul-07	BASIC SOLUTIONS WEED AND GRASS KILLER	07199500027 000239	DENVER	CO	HC	Unknown Adult (18-64 years old) Female applied the product for several weeks. She did not wear the proper personal protective equipment every time she uses the product. She reported Rash, Pruritus, Hives/Welts, Bullae/Blisters.
018859 001	01-Jul-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		TX	HC	Unknown Adult (18-64 years old) Female used the product. She inadvertently spilled a significant amount of the liquid all over her hands. She reported Tremor.
018860 001	01-Jul-07	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023		GA	HC	Unknown Adult (18-64 years old) Female used the product off and on for the past three months. She wears gloves when spraying, but the nozzle leaks and the liquid runs down the hose that touches her leg. She reported Numbness, Tingling.
018862 001	13-Jul-07	ROUNDUP WEED 7 GRASS KILLER READY-TO-USE	07199500032		NJ	HC	Unknown Adult (18-64 years old) Female used the product. She sprayed the product on and around the driveway on a hot day. She reported Chest Tightness, Pain.
018863 001	10-Jul-07	ROUNDUP READY-TO-USE EXTENDED CONTROL WEED & GRASS KILLER1 PLUS WEED P	07199500021		TN	HC	Unknown Adult (18-64 years old) Female sprayed the product and some got into her eye. She reported Ocular Irritation, Corneal Abrasion, and Blisters on her Eye.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report**

3/12/09

**Chemical: Glyphosate****103601****Human Incidents**

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
018865	001	24-Jul-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		MO	HC	Unknown Adult (18-64 years old) Female got a small amount of the product on her Face. The patient was diagnosed with Dehydration, Low Sodium, and Potassium.
018868	001	02-Jul-07	ROUNDUP HERBICIDE	00052400445		SC	HC	A 39 year old Female got sprayed in the eyes with the product while at work. She reported Ocular Irritation, Corneal Abrasion, and Irritation/Pain.
018869	001	31-Jul-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE PLUS	07199500033		WA	HC	Unknown Adult (18-64 years old) Female sprayed the product for about 45 minutes. After spraying the product some of it dripped on her hand. She reported Chest Tightness, Hoarseness, and Tingling Hands.
018870	001	17-Jun-07	TOTAL KILL PRO	00052400536			HC	Unknown Adult (18-64 years old) Male, who has a history of heart attacks, reported Dyspnea, Wheezing, Chest Tightness, and Severe Headache. The product spilled near his air conditioner outside.
018875	001	23-Jul-07	ROUNDUP HERBICIDE	00052400445		TX	HC	Unknown Adult (18-64 years old) Male applied the product which got on his pants. He continued to work and did not wash off the product for about 3-4 hours. He reported a Rash on his Scrotum.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report**

3/12/09

**Chemical: Glyphosate****103601****Human Incidents**

Incident Number	Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
018876 001	12-Jun-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE	07199500032		NY	HC	Unknown Adult (18-64 years old) Male was exposed while at work after someone sprayed a fence line with the product. He was nearby and felt some of the product get in his mouth. He reported Coughing, Sore Throat, and Difficulty Breathing.
018912 001	28-Aug-07	CREDIT SYSTEMIC HERBICIDE	07136800020		NY	HC	A 15 year old Male applied the product on a tree farm and the product splashed in his face. He reported Redness, Eye Swelling, Dermal Irritation, Corneal Abrasion, and Congestion.
018951 001	13-Aug-07	ROUNDUP WEED & GRASS KILLER READY-TO-USE PLUS	07199500033		LA	HC	Unknown Adult (18-64 years old) Male sprayed the product. He was diagnosed by his physician with an Upper Respiratory Tract Infection.
018957 001	01-Aug-07	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023	OZARKS		HC	A 73 year old Female sprayed her friend's driveway with the product and she did not wash after spraying. She reported a Rash.
018958 001	01-Aug-07	ROUNDUP SUPER CONCENTRATE WEED & GRASS KILLER 1	07199500018		NY	HC	Unknown Adult (18-64 years old) Male sprayed the product on his lawn. He reported Nausea, Dizziness, Fatigue and High Blood Pressure.
018963 001	01-Aug-07	ROUNDUP HERBICIDE	00052400445		FL	HC	Unknown Adult (18-64 years old) Male was nearby while a person applied the product on the side of a highway. He reported a Burning Throat and Lungs.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report**

3/12/09

**Chemical: Glyphosate****103601****Human Incidents**

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
019066	001	18-Sep-07	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	07199500023		NY	HC	Unknown Adult (18-64 years old) Female used the product for the first time for thirty minutes. She reported Burning Eyes, Itchy Skin.
019068	001	01-Jun-07	ROUNDUP HERBICIDE	00052400445		TN	HC	Unknown Adult (18-64 years old) Male, applied the product with a tank sprayer during the summer. He reported Chronic Coughing.
019186	001	13-Oct-07	ROUNDUP HERBICIDE	00052400445		GA	HC	A 73 year old Female used the product on the area around her pond that she cannot cut. She diluted the product and mixed it herself. She reported a Rash, Swollen Eyes.
019189	001	01-Sep-07	ROUNDUP WEED AND GRASS KILLER CONCENTRATE	07199500017		CA	HC	Unknown Adult (18-64 years old) Male used a back pack sprayer to apply the product. The back pack was leaking and the liquid ran down his back and pants. The man, who has a history of Diabetes, was diagnosed by a physician with Chemical Burns.
019244	001	08-Nov-07	ROUNDUP READY-TO-USE WEED & GRASS KILLER	07199500008		AZ	HC	A 39 year old Male purchased a bottle of a product and was transporting it in the front seat of his vehicle. The bottle spilled on his pants that removed about an hour later. He reported Peeling Skin.
019337	001	27-Nov-07	SHOOTOUT WEED & GRASS KILLER CONCENTRATE	06776000046 009688	FAYETTEVILLE	AR	HC	A 76 year old Male got the product on his hands. He reported Red Hands, Tingling Skin.

## Glyphosate Registration Review Human-Health Assessment Scoping Document

**IDS Report** 3/12/09**Chemical: Glyphosate****103601****Human Incidents**

Incident Number		Incident Date	Product Name	Registration Number	City	State	Exposure Type*	Incident Description
019363	001	01-Jun-07	POWER FORCE GRASS & WEED KILLER 1 GAL RTU	06776000061 072155	CINCINNATI	OH	HC	A 79 year old Male applied the product on his lawn and reported Erythema/Flushed, Pruritus.
019537	001	01-Nov-07	ROUNDUP HERBICIDE	00052400445		MD	HC	Unknown Adult (18-64 years old) Male was exposed to the product. The patient wore gloves but the product leaked through the gloves on his skin. He reported a Burning Sensation, Rash on both of his Hands, and Right Wrist.
019541	001	01-Mar-08	ROUNDUP WEED AND GRASS KILLER READY TO USE PLUS	07199500033		CA	HC	Unknown Adult (18-64 years old) Male used the product and reported Coughing, Twitching on the Left side of his body.
019726	001	01-Mar-08	ROUNDUP HERBICIDE	00052400445		HI	HC	Unknown Adult (18-64 years old) Male mixed the product got some of it on his hands. He reported Reddish Brown Hands, Discoloration, and Sensitive Skin.
019727	001	03-Jun-08	ROUNDUP PRO	00052400475		CA	HC	Unknown Adult (18-64 years old) Male, who is a landscaper, got the product in his eyes. He reported Redness, Eye Irritation.



Message

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**From:** HEYDENS, WILLIAM F [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=230737]  
**Sent:** 3/31/2016 11:34:45 PM  
**To:** JENKINS, DANIEL J [AG/1920] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=813004]; HEERING, DAVID C [AG/1000] [/O=MONSANTO/OU=NA-1000-01/cn=RECIPIENTS/cn=68681]; LISTELLO, JENNIFER J [AG/1000] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=533682]; REBMAN, JOHN [AG/1000] [/O=MONSANTO/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=JREBMc1a]  
**Subject:** Re: EPA glyphosate questions

Dan, will folks from HE'D be at this meeting?

----- Original Message -----

Subject: EPA glyphosate questions

From: "JENKINS, DANIEL J [AG/1920]" <daniel.j.jenkins@monsanto.com>

Date: Mar 31, 2016, 5:15 PM

To: "HEERING, DAVID C [AG/1000]" <david.c.heering@monsanto.com>, "HEYDENS, WILLIAM F [AG/1000]" <william.f.heydens@monsanto.com>, "LISTELLO, JENNIFER J [AG/1000]" <jennifer.j.listello@monsanto.com>, "REBMAN, JOHN [AG/1000]" <john.rebman@monsanto.com>

Dan Jenkins  
US Agency Lead  
Monsanto Company  
202 383 2851 (o)  
571 732 6575 (c)

Begin forwarded message:

**From:** "Nguyen, Khue" <Nguyen.Khue@epa.gov>

**Date:** March 31, 2016 at 5:27:43 PM EDT

**To:** "JENKINS, DANIEL J [AG/1920]" <daniel.j.jenkins@monsanto.com>

**Cc:** "Smith, Charles" <Smith.Charles@epa.gov>, "Anderson, Neil" <Anderson.Neil@epa.gov>, "Moriarty, Thomas" <Moriarty.Thomas@epa.gov>

**Subject:** meeting next week

Hi Dan,

I'm forwarding additional details from our human health folks about the meeting next week:

As part of Registration Review, the agency has been evaluating the extensive data that is available for glyphosate, including the IARC and EFSA reports on carcinogenicity. This has included a toxicological analysis consisting of a wide variety of experimental animal data and *in vitro* data from the guideline studies and from the scientific literature. In addition we are evaluating the

epidemiological database of about a dozen US and European studies. In order to better characterize the significant toxicological and epidemiological data that is available for glyphosate in the registration review preliminary risk assessment, the agency has been attempting to determine changes over the last 20 or 30 years in the use of glyphosate products over time (i.e., which formulations have dominated the market). EPA is also interested in how the inert compounds used in the major glyphosate products utilized in agricultural settings in the US and in Europe have changed over the last 20 or 30 years. The agency is particularly interested in utilizing this data to help characterize any potential differences in the US and European glyphosate epidemiology studies (mid 1980s – early 2000s, see list below). We would like to discuss this in more detail during next week's meeting.

List of glyphosate epidemiology studies:

De Roos, A. J., Blair, A., Rusiecki, J. A., Hoppin, J. A., Svec, M., Dosemeci, M., Alavanja, M. C. (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect*, 113(1), 49- 54.

De Roos, A. J., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Holmes, F. F., Burmeister, L. F., & Blair, A. (2003). Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med*, 60(9), E11.

Eriksson, M., Hardell, L., Carlberg, M., & Akerman, M. (2008). Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int J Cancer*, 123(7), 1657-1663.

Hardell, L., Eriksson, M., & Nordstrom, M. (2002). Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma*, 43(5), 1043- 1049.

McDuffie, H. H., Pahwa, P., Mclaughlin, J. R., Spinelli, J. J., Fincham, S., Dosman, J. A., Choi, N. W. (2001). Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev*, 10(11), 1155-1163.

Orsi, L., Delabre, L., Monnereau, A., Delval, P., Berthou, C., Fenaux, P., Clavel, J. (2009). Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. *Occupational and Environmental Medicine*, 66(5), 291-298.

111 De Roos, A. J., Blair, A., Rusiecki, J. A., Hoppin, J. A., Svec, M., Dosemeci, M., Alavanja, M. C. (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect*, 113(1), 49- 54.

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Orsi, L., Delabre, L., Monnereau, A., Delval, P., Berthou, C., Fenaux, P., Clavel, J. (2009) . Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. *Occupational and Environmental Medicine*, 66(5), 291-298.

Let me know if you have any questions.

Thanks,

Khue Nguyen  
Chemical Review Manager  
Risk Management and Implementation Branch 1  
Pesticide Re-evaluation Division  
Office of Pesticide Programs, EPA  
703-347-0248  
[Nguyen.khue@epa.gov](mailto:Nguyen.khue@epa.gov)

Message

**From:** Buelig, Mattias [Mattias.Buelig@fcs-feinchemie.com]  
**Sent:** 7/19/2012 10:18:12 AM  
**To:** GUSTIN, CHRISTOPHE [AG/5040] [/O=MONSANTO/OU=EA-5041-01/cn=Recipients/cn=83930]; Pepita Duran [duran@gtaduran.com]; GARNETT, RICHARD P [AG/5040] [/O=MONSANTO/OU=EA-5041-01/cn=Recipients/cn=107838]; sylvain.gautier@arystalifescience.com; 'Annette Salomonsen' [annette.salomonsen@cheminova.com]; CARONE@dow.com; eric.gibert@at.nufarm.com; nikolaus.zenz@syngenta.com; egay@afresa.es; mihailova@agria.bg; 'Bob Nicholls' [Bob.Nicholls@Laronkarn.co.uk]; a.lang@agrotrade.de; jward@etracom.com; c.vanesbroeck@agrifchem.nl; ian@barclay.ie; 'Slawomir Kijowski' [slawomir.kijowski@bros.pl]; ravikumar@excelcropcare.com; f.thuerwaechter@helmag.com; franka.peric@pinus-tki.si; ftroubac@rotam.com; 'Shalaka Shelar' [shalaka.shelar@sabero.com]; monique.bourdin@sfp-rd.com; npear@uk.exponent.com; aduarte@agro.saptec.pt; bgoswami@uniphos.com; tina\_wang@wynca.com  
**CC:** 'Martyn Hargraves' [t9c@live.co.uk]; GRAHAM, WILLIAM [AG/5432] [/O=MONSANTO/OU=EA-5040-01/cn=Recipients/cn=233911]; HEYDENS, WILLIAM F [AG/1000] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=230737]; SALTMIRAS, DAVID A [AG/1000] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=DASALT]; GARNETT, RICHARD P [AG/5040] [/O=MONSANTO/OU=EA-5041-01/cn=Recipients/cn=107838]  
**Subject:** AW: Genotox Review: your approval requested!

Dear Christophe,

FCS agrees to the additional costs as well.

Best regards,

Mattias

**Von:** GUSTIN, CHRISTOPHE (AG/5040) [mailto:christophe.gustin@monsanto.com]

**Gesendet:** Mittwoch, 18. Juli 2012 19:12

**An:** GUSTIN, CHRISTOPHE (AG/5040); Pepita Duran; GARNETT, RICHARD P (AG/5040); sylvain.gautier@arystalifescience.com; 'Annette Salomonsen'; CARONE@dow.com; Buelig, Mattias; eric.gibert@at.nufarm.com; nikolaus.zenz@syngenta.com; egay@afresa.es; mihailova@agria.bg; 'Bob Nicholls'; a.lang@agrotrade.de; jward@etracom.com; c.vanesbroeck@agrifchem.nl; ian@barclay.ie; 'Slawomir Kijowski'; ravikumar@excelcropcare.com; f.thuerwaechter@helmag.com; franka.peric@pinus-tki.si; ftroubac@rotam.com; 'Shalaka Shelar'; monique.bourdin@sfp-rd.com; npear@uk.exponent.com; aduarte@agro.saptec.pt; bgoswami@uniphos.com; tina\_wang@wynca.com

**Cc:** 'Martyn Hargraves'; GRAHAM, WILLIAM (AG/5432); HEYDENS, WILLIAM F (AG/1000); SALTMIRAS, DAVID A (AG/1000); GARNETT, RICHARD P (AG/5040)

**Betreff:** Genotox Review: your approval requested!

**Wichtigkeit:** Hoch

URGENT REQUEST

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Dear RWG,

As part of the GTF literature review the RWG and Board agreed to ask Larry Kier (former Monsanto expert and now independent consultant) to write a genotox review paper on technical glyphosate and glyphosate based Plant Protection Products. This paper would pool data from confidential Taskforce Member studies which was the reason why David Saltmiras (MON), chair to the tox-TWG, stepped down as a co-author for this paper. In addition when trying to combine both reviews (on technical glyphosate and PPPs) the manuscript turned into such a large mess of studies reporting genotoxic effects, that the story as written stretched the limits of credibility among less sophisticated audiences. For most 'stories', the approach would have been fine. But even though we feel confident that glyphosate is not genotoxic, this became a very difficult story to tell given all the complicated 'noise' out there. So David Saltmiras, Larry Kier and Bill Heydens consulted by other Monsanto tox experts thought there was a need to re-group & redesign the approach to the manuscript.

The suggested approach was to split-up the reviews in 2 papers (one on tech glyphosate and one on PPPs). In addition it was suggested that one way to help enhance credibility is to have an additional author on the papers who is a renowned specialist in the area of genotoxicity. Larry Kier did a search for possible co-authors and came up with 5. After internal discussion and some checking by David Saltmiras with fellow TWG tox folks (see extracts from TWG-meeting minutes below), Dr. David Kirkland was identified as the best candidate.

David Kirkland is an independent consultant with a history at Covance Laboratories. He is an expert in 'COMET'-assays on PPPs and is member of the editorial board for 'Mutagen Research' and member of the Environmental Mutagen Society in the UK. David Kirkland would most definitely add substantial expertise and credibility to this critical paper.

The initial cost estimate for this manuscript was 9k\$ (approved by the board).

Adding David Kirkland as a co-author to both review papers would add £14,000 (pounds Stirling) to the project, which split by 25 seems a fair investment.

Please let me know as soon as possible if we have your support to proceed with David Kirkland as a co-author. We need a decision soon since David Kirkland only has the month of August to work on the papers.

David, Bill, please let me know if I missed or misinterpreted something.

Best regards,

Christophe.

**From:** SALTMIRAS, DAVID A [AG/1000]  
**Sent:** Wednesday, July 18, 2012 4:54 PM  
**To:** GUSTIN, CHRISTOPHE [AG/5040]  
**Subject:** RE: Genotox Review

Christophe,

Below are extracts from recent meeting minutes this month. David Kirkland was discussed as a strong candidate to coauthor on July 2<sup>nd</sup> and ToxTWG endorsed him on July 16<sup>th</sup> and plans to engage him were put in motion.

- From July 2<sup>nd</sup>
  - a. Genotoxicity review manuscript.
    - i. Discussed approaches for literature and data reviews
    - ii. Consensus gained for two companion papers on active ingredient and formulated product genotoxicity data (GTF member company data and peer reviewed publications)
    - iii. **Co-authors with Larry Kier were discussed. David Kirkland was proposed as strong candidate for this role.** Syngenta proposed Barry Elliott, expressing possible bias towards COMET assay data by David Kirkland. Simon will inquire within the Syngenta genotox group on suitability of David Kirkland to provide an objective scientific review including weight of evidence for the full data set (GTF member study reports and peer reviewed publications).
      - **NOTE:** Larry had contacted David Kirkland yesterday to discuss the paper and Larry contacted David Saltmiras today (Tuesday July 3<sup>rd</sup>) to debrief.
      - Larry is convinced that David Kirkland will provide a strong technical skill set to evaluate the breadth of data including the COMET data (weighing convenience of

COMET assays with credible data interpretability) and believes David Kirkland would be an excellent choice to co-author the manuscript.

- David Kirkland is available to work on this project in August/Sept and submit to the journal by the end of September.
- iv. Still targeting *Critical Reviews in Toxicology*, based on the length of these papers.
  - Larry has briefly discussed with the chief editor of *Critical Reviews in Toxicology* (Roger McClellan), who expressed concern that the GTF member study reports are not public (weighing in on negative genotox results) vs the publication record (weighing in on positive genotox results). This will present itself as an issue with any credible journal. To have credibility, rather than make all study reports public, the GTF may consider submitting all the genotoxicity study Tier II Summaries from the dossier (which may well fall into the public domain) as supplementary data to the journal.
  - **Please email David Saltmiras regarding this approach of submitting the TIS for genotox studies as supplementary data if your company owns genotoxicity data.**

- From July 16<sup>th</sup>

2. Genotoxicity review manuscript

- a. David Saltmiras will circulate contact information for David Kirkland for individual companies to arrange CDAs (Arysta LifeScience, Cheminova, Excel Crop Care, Feinchemie Schwebda, Helm, Nufarm, Syngenta).
- b. Data for manuscript
  - i. General agreement was reached to provide member company study methodology and data summaries as supplementary information in support of publications on (i) active substance and (ii) formulated products.
  - ii. Study summaries and citations should be sanitized to exclude
    - Study director names

- Data owner/company name
  
- iii. Study summaries and citations may include
  - Study/report number
  - Study/report title
  - Year of study/report
  - Performing laboratory (not necessary, sometimes deleted/sanitized for public information like DARs)
  - Test substance purity (for active substance)
  - Formulation type (for formulated product)
  - Note of whether GLP or non-GLP
  - Test Guideline(s) followed (OECD/US EPA, JMAFF, etc.)
  - Brief description of methodology
  - Summarized data tables
  
- iv. Transfer of study information between coauthors
  - Larry Kier needs to email a rider/CDA amendment for each company to grant him permission to share data with David Kirkland.
  - Larry Kier and David Kirkland should sign a CDA with eachother.

*David Saltmiras, Ph.D., D.A.B.T.*  
Toxicology Manager  
Regulatory Product Safety Center  
Monsanto  
ph (314) 694-8856

**From:** GUSTIN, CHRISTOPHE [AG/5040]  
**Sent:** Wednesday, July 18, 2012 9:40 AM  
**To:** SALTMIRAS, DAVID A [AG/1000]

**Cc:** GARNETT, RICHARD P [AG/5040]; HEYDENS, WILLIAM F [AG/1000]

**Subject:** RE: Genotox Review

Will do!!

**From:** SALTMIRAS, DAVID A [AG/1000]

**Sent:** Wednesday, July 18, 2012 3:47 PM

**To:** GUSTIN, CHRISTOPHE [AG/5040]

**Cc:** GARNETT, RICHARD P [AG/5040]; HEYDENS, WILLIAM F [AG/1000]

**Subject:** FW: Genotox Review

**Importance:** High

Christophe,

Will you please take this to the RWG ASAP? At this point we have an open Monsanto contract with David Kirkland, CDA's with individual member companies are being initiated and Larry Kier plans to get a draft manuscript to him by the end of the month (i.e. in less than 2 weeks). Kirkland is only available to work in this project in August and approval of his involvement is strongly recommended by the ToxTWG. If our time lines slip on this we will probably not have a genotoxicity review manuscript available for our submission window in January.

Is there a way to get this through the RWG in a week?

Thanks,

*David Saltmiras, Ph.D., D.A.B.T.*

Toxicology Manager

Regulatory Product Safety Center

Monsanto

ph (314) 694-8856

**From:** GRAHAM, WILLIAM [AG/5432]

**Sent:** Wednesday, July 18, 2012 8:24 AM

**To:** HEYDENS, WILLIAM F [AG/1000]; SALTMIRAS, DAVID A [AG/1000]; GUSTIN, CHRISTOPHE [AG/5040]; GARNETT, RICHARD P [AG/5040]

**Cc:** LEMKE, SHAWNA LIN [AG/1000]; KRONENBERG, JOEL M [AG/1000]

**Subject:** RE: Genotox Review

I think it has to go through the normal process- TWG to RWG to Board, with documented agreement at each stage. Once the RWG has agreed we can do the Board by email.

I think Bill H's summary could be a good basis for getting RWG alignment.

BillG

**From:** HEYDENS, WILLIAM F [AG/1000]

**Sent:** Tuesday, July 17, 2012 5:54 PM

**To:** GRAHAM, WILLIAM [AG/5432]; SALTMIRAS, DAVID A [AG/1000]; GUSTIN, CHRISTOPHE [AG/5040]; GARNETT, RICHARD P [AG/5040]

**Cc:** LEMKE, SHAWNA LIN [AG/1000]; KRONENBERG, JOEL M [AG/1000]

**Subject:** RE: Genotox Review

Bill,

David & I were just touching base on a couple things, and we were wondering what your thinking is on how to progress this with the Board – let us know – thanks.

Bill

**From:** HEYDENS, WILLIAM F [AG/1000]

**Sent:** Friday, July 13, 2012 1:09 PM

**To:** HEYDENS, WILLIAM F [AG/1000]; GRAHAM, WILLIAM [AG/5432]; SALTMIRAS, DAVID A [AG/1000]; GUSTIN, CHRISTOPHE [AG/5040]; GARNETT, RICHARD P [AG/5040]

**Cc:** LEMKE, SHAWNA LIN [AG/1000]; KRONENBERG, JOEL M [AG/1000]

**Subject:** RE: Genotox Review

Bill,

Here is my further perspective on top of David's...

As David notes, we are still essentially talking about lines 12 & 13 on the Excel spreadsheet you sent. David embarked on the Genotox publication work with Larry Kier as agreed by the Board.

But here is what transpired after that. After they got all the studies amassed into a draft manuscript, it unfortunately turned into such a large mess of studies reporting genotoxic effects, that the story as written stretched the limits of credibility among less sophisticated audiences. For most 'stories', the approach would have been fine. But even though we feel confident that glyphosate is not genotoxic, this became a very difficult story to tell given all the complicated 'noise' out there. So we (David, Larry, Bill H, Joel & Shawna) thought we needed to re-group & redesign the approach to the manuscript. As part of that re-tooling approach, it was suggested that one way to help enhance credibility is to have an additional author on the paper who is a heavy-hitter in the area of genotoxicity. Larry did a search for possible co-authors and came up with 5. After internal discussion and some checking by David with fellow TWG tox folks, we landed on Kirkland as the best candidate. That has led to the request you have before you.

So if you think there needs to be a discussion with the Board rather than trying to gain approval via e-mail, then we could take that approach, but this obviously slows down the process. Is there a Board phone conference scheduled anytime soon?

Bill

**From:** HEYDENS, WILLIAM F [AG/1000]

**Sent:** Friday, July 13, 2012 11:20 AM

**To:** GRAHAM, WILLIAM [AG/5432]; SALTIRAS, DAVID A [AG/1000]; GUSTIN, CHRISTOPHE [AG/5040]; GARNETT, RICHARD P [AG/5040]

**Subject:** RE: Genotox Review

Bill, I have to run to a meeting, but I will give you my perspective later today when you are drinking G&Ts.

**From:** GRAHAM, WILLIAM [AG/5432]

**Sent:** Friday, July 13, 2012 11:17 AM

**To:** SALTMIRAS, DAVID A [AG/1000]; GUSTIN, CHRISTOPHE [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; GARNETT, RICHARD P [AG/5040]

**Subject:** RE: Genotox Review

There is a lot of information here which the Board has not seen ( to my knowledge) . The discussion of published summaries took place at the 13<sup>th</sup> Meeting (March 2012) and I attach the information which was presented and agreed ( according to the Minutes). I think you will agree that the current situation needs to go to the Board for a second discussion and updated Agreement.

If Richard or Bill H have any additional information about the Board discussions on this subject then I will gladly change my opinion.

Bill

**From:** SALTMIRAS, DAVID A [AG/1000]

**Sent:** Friday, July 13, 2012 3:48 PM

**To:** GRAHAM, WILLIAM [AG/5432]; GUSTIN, CHRISTOPHE [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; GARNETT, RICHARD P [AG/5040]

**Subject:** RE: Genotox Review

Bill,

Two different projects have been merged, the first of which was well underway before the PAG was instituted. The initial project was a review manuscript of the glyphosate genotoxicity literature authored by Larry Kier and me (authorized Feb 22, 2011 for \$9,000). The second (initiated by the PAG and supported by the RWG and Board, cost estimate of \$13,195) was a review manuscript involving all glyphosate genotoxicity studies owned by GTF member companies on both active ingredient and formulated products, authored by Larry; the review of GTF members' proprietary study reports prohibit my coauthorship.

This first became a very long and tedious manuscript, which would have been difficult to publish. Following on from this first draft manuscript review, discussions with Bill H., Joel, me and Larry Kier resulted in a merging of the two projects (also discussed at the ToxTWG) with a view to publish two companion manuscripts on glyphosate genotoxicity for the active ingredient (paper 1) and formulated products (paper 2). Thus Larry was

the sole author and given his geography and industry alignment, other highly credible genotoxicologists coauthors from European were sought. David Kirkland was the first choice of the GTF ToxTWG.

David Kirkland's expertise comes at a premium. I believe Larry Kier significantly under charges for his services, but his combined cost estimate for project 1 and project 2 is \$22,195. David Kirkland believes his efforts will be less than 10 days at £1,400/day (equivalent to \$21,780 with the current exchange rate), so we are effectively doubling the cost of the combined projects, but reaping significant value/credibility from David Kirkland's involvement. Given the growing number of questionable genotoxicity publications, in my mind this is worth the addition cost.

I have subsequently coordinated an open master contract between Monsanto and David Kirkland (we may need his services in the future) and on the next ToxTWG call (Monday) will request all member companies get confidentiality agreements in place with him ASAP (the same CDAs as previously signed with Larry Kier, enabling him to see their study reports).

*David Saltmiras, Ph.D., D.A.B.T.*

Toxicology Manager  
Regulatory Product Safety Center  
Monsanto  
ph (314) 694-8856

**From:** GRAHAM, WILLIAM [AG/5432]

**Sent:** Friday, July 13, 2012 9:01 AM

**To:** GUSTIN, CHRISTOPHE [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; SALTMIRAS, DAVID A [AG/1000]; GARNETT, RICHARD P [AG/5040]

**Subject:** Genotox Review

The project was initiated by the PAG and supported by the RWG and Board. The cost was \$9k and I thought the job had been completed. The name "David Kirkland" has never come to my attention before and I would suggest that the RWG needs to explain to the Board why, at this point, it believes that trebling the expenditure to include a second author is a justifiable expense.

I wonder if this is a true PAG project where those companies who want to see this work carried out pay for it.

I have received questions about future expenditure and I cannot see it on Richard's list which went to the Board for approval/discussion last month.

Bill

**From:** GUSTIN, CHRISTOPHE [AG/5040]  
**Sent:** Friday, July 13, 2012 2:04 PM  
**To:** HEYDENS, WILLIAM F [AG/1000]; SALTMIRAS, DAVID A [AG/1000]  
**Cc:** GRAHAM, WILLIAM [AG/5432]; GARNETT, RICHARD P [AG/5040]  
**Subject:** RE: A FedEx shipment [793774060139] was created.

Hi Bill,

The proposal sounds very reasonable and having David Kirkland co-authoring this paper can only strengthen the case. Since the board has approved the project I agree it makes sense to ask the board directly to approve the extra funding. It I don't seem to remember this (adding Kirkland) being discussed at RWG level but could be wrong. If not I'll send out an update message to make sure everyone is on the same page.

Regards,

C.

**From:** HEYDENS, WILLIAM F [AG/1000]  
**Sent:** Thursday, July 12, 2012 10:52 PM  
**To:** SALTMIRAS, DAVID A [AG/1000]; GUSTIN, CHRISTOPHE [AG/5040]  
**Cc:** GRAHAM, WILLIAM [AG/5432]; GARNETT, RICHARD P [AG/5040]  
**Subject:** RE: A FedEx shipment [793774060139] was created.

Christophe,

We (David, Joel, Kier, me) think we should proceed with pursuing Kirkland as a co-author for the glyphosate genotox publication. David also got some other toxicologist feedback from within the Tox TWG and that was favorable as well.

So how should we proceed? For expediency, since this project is already supported by the Board, could we have Bill go directly to the Board by sending out a note asking them to approve contracting with Kirkland for an estimated maximum amount of £14,000?

Thanks.

Bill

**From:** SALTMIRAS, DAVID A [AG/1000]  
**Sent:** Thursday, July 12, 2012 11:03 AM  
**To:** HEYDENS, WILLIAM F [AG/1000]; GUSTIN, CHRISTOPHE [AG/5040]  
**Subject:** FW: A FedEx shipment [793774060139] was created.

Bill & Christophe,

We (Monsanto) have a signed master contract with David Kirkland. This will enable him to coauthor the genotoxicity review paper with Larry Kier, as well as engaging him on any other projects which may come up... it may be necessary to have an EU based expert in genotoxicity on hand if issues arise during the regulatory review.

Please note David's estimated cost, below, which will need GTF board approval....he thinks likely less than 10 days work (at £1,400/day).

*David Saltmiras, Ph.D., D.A.B.T.*  
Toxicology Manager  
Regulatory Product Safety Center

Monsanto  
ph (314) 694-8856

**From:** David Kirkland [<mailto:root@genetoxconsulting.co.uk>]  
**Sent:** Thursday, July 12, 2012 10:49 AM  
**To:** SALTMIRAS, DAVID A [AG/1000]  
**Subject:** RE: A FedEx shipment [793774060139] was created.

David,

Daily rate is equivalent to 8 hours, namely GBP1400 per day.

I estimate a maximum of 10 days (i.e. GBP14,000) but unless I have to delve very deeply into a lot of the reports and papers that Larry includes, it should be less than this.

Kind regards,

David.

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Feinchemie Schwebda GmbH  
Edmund-Rumpler-Str. 6  
51149 Koeln

Geschaeftsfuehrer: Dr. Gerhard Ahlers  
Amtsgericht Koeln HRB 66957

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Message

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**From:** WAKIMORI, HIROO [AG/5270] [/O=MONSANTO/OU=AP-5340-01/CN=RECIPIENTS/CN=155939]  
**Sent:** 6/1/2016 7:40:30 AM  
**To:** JACKSON - GHEISSARI, AMELIA ELIZABETH [AG/1920] [/O=MONSANTO/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=AEJACK196e]; Nguyen, Khue [Nguyen.Khue@epa.gov]  
**CC:** JENKINS, DANIEL J [AG/1920] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=813004]; Moriarty, Thomas [Moriarty.Thomas@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]; Lowit, Anna [Lowit.Anna@epa.gov]; Smith, Charles [Smith.Charles@epa.gov]; GARNETT, RICHARD P [AG/5040] [/O=MONSANTO/OU=EA-5041-01/cn=Recipients/cn=107838]; LISTELLO, JENNIFER J [AG/1000] [/O=MONSANTO/OU=NA-1000-01/cn=Recipients/cn=533682]  
**Subject:** RE: glyphosate TAC

Hello Amelia,

TAC is OK for Monsanto to provide the English translation of the draft Assessment Report of Glyphosate by Food Safety Commission. The following links to the folder of Glyphosate draft Assessment Report in Japanese at Food Safety Commission site.

[資料4 : グリホサート農薬評価書 \(案\) \[PDF:4,121KB\]](#)

Monsanto started translation of these documents in late March and I have just received a draft translation. It will take at least a few more weeks for me to edit and finalize this 300 page document which covers all toxicology studies of 5 data sets. I will let you and all cc'd know when the translation is ready for your reading probably in the week of June 20<sup>th</sup>.

Thanks and regards,

Hiroo Wakimori

\*\*\*\*\*

Hiroo Wakimori

Chemistry Technical Lead, Asia

Monsanto Japan Limited

Kyobashi Souseikan 6F

2-5-18 Kyobashi, Chuo-ku

Tokyo 104-0031 JAPAN

+81-3-6264-4856(Work)

+81-3-3566-5411(Fax)

+81-80-2113-9417(Mobile)

E mail: hiroo.wakimori@monsanto.com

\*\*\*\*\*

**From:** JACKSON - GHEISSARI, AMELIA ELIZABETH [AG/1920]

**Sent:** Wednesday, June 01, 2016 1:18 AM

**To:** Nguyen, Khue

**Cc:** JENKINS, DANIEL J [AG/1920]; Moriarty, Thomas; Anderson, Neil; Lowit, Anna; Smith, Charles; WAKIMORI, HIROO [AG/5270]; GARNETT, RICHARD P [AG/5040]; LISTELLO, JENNIFER J [AG/1000]

**Subject:** RE: glyphosate TAC

Dear Khue,

Dr Hiroo Wakimori in our Japan office will help you with the TAC studies. Again, for those studies for which we are not the owners we can't do more than put you in touch with the owners.

Dr Wakimori will ask TAC if the English translation of Japan's Food Safety Commission (FSC) Assessment Report can be supplied to the EPA. The FSC Assessment Report is available on line only in Japanese. If OK with TAC, Dr Wakimori will provide the translation to you. Also, the JMPR will soon publish a detailed report of the recently completed Extraordinary Review which should contain a review of TAC studies.

If you want access to the full studies/TAC data, you may want to ask directly to the TAC group members for help. We can introduce the relevant TAC contact people (it would be company by company).

Hope this helps.

Dr Wakimori can be contacted on +81 3 6264 4856. He is also copied on this email.

Best wishes,

Amelia

Amelia Jackson-Gheissari PhD

International Regulatory Affairs Manager

Monsanto Company

1300 I Street , NW

Suite 450 East

Washington DC 20005

Office: +1 202 383 2847

Cell: +1 202 230 6733

**From:** Nguyen, Khue [<mailto:Nguyen.Khue@epa.gov>]

**Sent:** Monday, May 23, 2016 12:06 PM

**To:** JACKSON - GHEISSARI, AMELIA ELIZABETH [AG/1920]

**Cc:** JENKINS, DANIEL J [AG/1920]; Moriarty, Thomas; Anderson, Neil; Lowit, Anna; Smith, Charles

**Subject:** glyphosate

Hi Amelia,

Anna Lowit gave me your contact information, I hope you don't mind me emailing. I understand that you spoke briefly with Anna at the recent PPDC meeting about the possibility of getting European cancer data for glyphosate—particularly the data that EPA recently requested which were submitted to BfR. We were wondering if you've had a chance to look into this possibility? Is there someone over in Europe that we should contact?

Any insight or assistance you could provide would be greatly appreciated.

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

[Nguyen.khue@epa.gov](mailto:Nguyen.khue@epa.gov)

**HEYDENS, WILLIAM F [AG/1000]**

---

**From:** HEYDENS, WILLIAM F [AG/1000]  
**Sent:** Thursday, February 05, 2015 2:25 PM  
**To:** KOCH, MICHAEL S [AG/1000]; KOCH, MICHAEL S [AG/1000]; FARMER, DONNA R [AG/1000]; SALTMIRAS, DAVID A [AG/1000]; GARNETT, RICHARD P [AG/5040]; GUSTIN, CHRISTOPHE [AG/5040]  
**Cc:** LISTELLO, JENNIFER J [AG/1000]  
**Subject:** IARC Planning  
**Attachments:** Work Plan .xlsx

All,

Attached is an updated spreadsheet for our IARC preparations – we have come a long way already!  
Please let me know if you have any additions/corrections. Ongoing Activities are indicated by light blue fill color.

At our next IARC Planning meeting Monday, I would like us to turn our attention to next publications (new Meta-analysis & WoE/Plausibility paper) – how should we go about doing them, who does what, start working up costs, etc.

Please let me know if you have other ideas or comments.

Thanks.

Bill

**HEYDENS, WILLIAM F [AG/1000]**

---

**From:** HEYDENS, WILLIAM F [AG/1000]  
**Sent:** Tuesday, February 17, 2015 4:53 PM  
**To:** KOCH, MICHAEL S [AG/1000]; FARMER, DONNA R [AG/1000]; SALTMIRAS, DAVID A [AG/1000]; GARNETT, RICHARD P [AG/5040]; GUSTIN, CHRISTOPHE [AG/5040]; LISTELLO, JENNIFER J [AG/1000]  
**Cc:** HEYDENS, WILLIAM F [AG/1000]  
**Subject:** IARC Planning  
**Attachments:** Work Plan .xlsx

All,

Attached is an updated spreadsheet for our IARC preparations.

Please let me know if you have any additions/corrections. Ongoing Activities are indicated by light blue fill color.

We did not have our IARC Planning meeting Monday due to the site being closed. However, Donna and I had a phone conference with John Acquavella today, and this resulted in several additions which are on page 4 of the attached Work Plan document.

Please let me know if you have other ideas or comments.

Thanks.

Bill

**HEYDENS, WILLIAM F [AG/1000]**

---

**From:** HEYDENS, WILLIAM F [AG/1000]  
**Sent:** Tuesday, February 17, 2015 4:53 PM  
**To:** KOCH, MICHAEL S [AG/1000]; FARMER, DONNA R [AG/1000]; SALTMIRAS, DAVID A [AG/1000]; GARNETT, RICHARD P [AG/5040]; GUSTIN, CHRISTOPHE [AG/5040]; LISTELLO, JENNIFER J [AG/1000]  
**Cc:** HEYDENS, WILLIAM F [AG/1000]  
**Subject:** IARC Planning  
**Attachments:** Work Plan .xlsx

All,

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We did not have our IARC Planning meeting Monday due to the site being closed. However, Donna and I had a phone conference with John Acquavella today, and this resulted in several additions which are on page 4 of the attached Work Plan document.

Please let me know if you have other ideas or comments.

Thanks.

Bill

**HEYDENS, WILLIAM F [AG/1000]**

---

**From:** SALTMIRAS, DAVID A [AG/1000]  
**Sent:** Thursday, February 19, 2015 4:01 PM  
**To:** HEYDENS, WILLIAM F [AG/1000]; FARMER, DONNA R [AG/1000]  
**Cc:** KOCH, MICHAEL S [AG/1000]; HODGE-BELL, KIMBERLY C [AG/1000]  
**Subject:** RE: IARC Planning

Bill et al.,

I had an extended chat with Roger this afternoon, as is the custom. He said that Critical Reviews has already dedicated some significant space to the glyphosate topic, especially the pending issue #3 with both the carc paper & Kier paper. However, to the contrary, he did say he'd consider something along the lines of the 1, 3 – butadiene issue... I think we would have to prepare a very compelling story.

*David Saltmiras, Ph.D., D.A.B.T.*  
Science Fellow  
Novel Chemistry and Microbials Product Lead  
Toxicology and Nutrition Center  
Monsanto  
ph (314) 694-8856

---

**From:** HEYDENS, WILLIAM F [AG/1000]  
**Sent:** Thursday, February 19, 2015 7:53 AM  
**To:** FARMER, DONNA R [AG/1000]  
**Cc:** KOCH, MICHAEL S [AG/1000]; SALTMIRAS, DAVID A [AG/1000]; HODGE-BELL, KIMBERLY C [AG/1000]  
**Subject:** RE: IARC Planning

Donna,

Per our phone call with John the other day, the next two most important things that we need to do are the Meta-analysis publication and the Ag Health Study Follow-up publication, assuming we can get our hands on the data in a reasonable timeframe. I feel confident that we will have organizational support for doing these projects, so I think we need to start setting them up now.

For the meta-analysis, please contact Elizabeth, let her know we would like her/Ellen to do this, and get a cost estimate from her.

For the AHS data, I heard 2 action items during our call: first - get with the lawyers to initiate the FOI process; second - contact Tom Sorohan and get him lined up to do the analysis when we get the data; also, get a cost estimate from him.

For the overall plausibility paper that we discussed with John (where he gave the butadiene example), I'm still having a little trouble wrapping my mind around that. If we went full-bore, involving experts from all the major areas (Epi, Tox, Genetox, MOA, Exposure - not sure who we'd get), we could be pushing \$250K or maybe even more. A less expensive/more palatable approach might be to involve experts only for the areas of contention, epidemiology and possibly MOA (depending on what comes out of the IARC meeting), and we ghost-write the Exposure Tox & Genetox sections. An option would be to add Greim and Kier or Kirkland to have their names on the publication, but we would be keeping the cost down by us doing the writing and they would just edit & sign their names so to speak. Recall that is how we handled Williams Kroes & Munro, 2000.

One thing we could do now on this is to contact Roger McClellan at CRC and see if they would be amenable to putting this publication in *Crit. Rev. Toxicol.* John said he knew that Roger had done such a publication in the past. David, since you have worked with Roger on the other papers, would you be willing to contact him to judge his willingness to publish such a paper?

Any other thoughts welcomed.

Bill

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**From:** HEYDENS, WILLIAM F [AG/1000]  
**Sent:** Tuesday, February 17, 2015 4:53 PM  
**To:** KOCH, MICHAEL S [AG/1000]; FARMER, DONNA R [AG/1000]; SALTMIRAS, DAVID A [AG/1000]; GARNETT, RICHARD P [AG/5040]; GUSTIN, CHRISTOPHE [AG/5040]; LISTELLO, JENNIFER J [AG/1000]  
**Cc:** HEYDENS, WILLIAM F [AG/1000]  
**Subject:** IARC Planning

All,

Attached is an updated spreadsheet for our IARC preparations. Please let me know if you have any additions/corrections. Ongoing Activities are indicated by light blue fill color.

We did not have our IARC Planning meeting Monday due to the site being closed. However, Donna and I had a phone conference with John Acquavella today, and this resulted in several additions which are on page 4 of the attached Work Plan document.

Please let me know if you have other ideas or comments.

Thanks.

Bill

**HEYDENS, WILLIAM F [AG/1000]**

---

**From:** Mette K. Jensen [mette.jensen@cheminova.com]  
**Sent:** Monday, February 23, 2015 8:10 AM  
**To:** FARMER, DONNA R [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; 'Christian.Strupp@de.adama.com'; 'Thomas Sorahan'; SALTMIRAS, DAVID A [AG/1000]; HODGE-BELL, KIMBERLY C [AG/1000]; KOCH, MICHAEL S [AG/1000]  
**Cc:** Kimberly Bell  
**Subject:** RE: IARC Meeting 112  
**Attachments:** WorkingSchedule-Vol.112.doc

Dera Donna and All

Thank you for the very useful discussion;

It was nice speaking to you all and I look forward to meeting Thomas and Christian in person.

Please find attached the more detailed draft working schedule that I received from Kathryn Guyton.

In line with what Thomas said, Kathryn pointed out that the working schedule may change depending on the progress of the Working Groups.

She also said that " We'd be grateful if you could let us know your attendance plans",

I interpret this as if although we are free to attend any of the sessions as observers, the IARC would nevertheless appreciate to know our plans beforehand. Christian and Thomas, is it also your experience that we should let IARC know in advance which sessions we plan to attend?

best regards

Mette

**Mette Kirstine Boye Jensen**

Cheminova A/S

Senior Regulatory Scientist - Toxicology - Direct +45 9690 9775

---

**From:** FARMER, DONNA R [AG/1000] [mailto:[donna.r.farmer@monsanto.com](mailto:donna.r.farmer@monsanto.com)]  
**Sent:** 23. februar 2015 04:26  
**To:** FARMER, DONNA R [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; 'Christian.Strupp@de.adama.com'; 'Thomas Sorahan'; Mette K. Jensen; SALTMIRAS, DAVID A [AG/1000]; HODGE-BELL, KIMBERLY C [AG/1000]; KOCH, MICHAEL S [AG/1000]  
**Cc:** Kimberly Bell  
**Subject:** RE: IARC Meeting 112

-----Original Appointment-----

**From:** FARMER, DONNA R [AG/1000]  
**Sent:** Wednesday, February 18, 2015 8:59 AM  
**To:** FARMER, DONNA R [AG/1000]; HEYDENS, WILLIAM F [AG/1000]; 'Christian.Strupp@de.adama.com'; 'Thomas Sorahan'; 'Mette K. Jensen'; SALTMIRAS, DAVID A [AG/1000]; HODGE-BELL, KIMBERLY C [AG/1000]; KOCH, MICHAEL S [AG/1000]  
**Cc:** Kimberly Bell  
**Subject:** IARC Meeting 112  
**When:** Monday, February 23, 2015 7:00 AM-8:00 AM (UTC-06:00) Central Time (US & Canada).  
**Where:** Conf Call

**HEYDENS, WILLIAM F [AG/1000]**

---

**From:** John Acquavella [acquajohn@gmail.com]  
**Sent:** Monday, February 23, 2015 5:12 PM  
**To:** FARMER, DONNA R [AG/1000]  
**Cc:** HEYDENS, WILLIAM F [AG/1000]  
**Subject:** Re: IARC Meeting 112

Donna/Bill:

The schedule looks favorable. Since it will be Thursday before the workgroup starts to discuss the glyphosate draft and I assume Tom will get a copy of the glyphosate draft on Tuesday, Tom will have time to assess the key issues and give us a read on the draft before the initial IARC discussions. That would provide time to give any support he thinks necessary.

John

On Feb 23, 2015, at 1:00 PM, FARMER, DONNA R [AG/1000]  
<[donna.r.farmer@monsanto.com](mailto:donna.r.farmer@monsanto.com)> wrote:

We had a conf call this morning with the 3 observers and the attached schedule was provided to the Mette Jensen the observer from Cheminova, Tom received a more generic schedule and Christian Strupp from ADAMA did not receive anything.

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<WorkingSchedule-Vol.112.doc>

Message

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**From:** GARNETT, RICHARD P [AG/5040] [/O=MONSANTO/OU=EA-5041-01/CN=RECIPIENTS/CN=107838]  
**Sent:** 10/10/2013 2:41:59 PM  
**To:** WAKIMORI, HIROO [AG/5270] [/O=MONSANTO/OU=AP-5340-01/CN=RECIPIENTS/CN=155939]; SALTMIRAS, DAVID A [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=DASALT]  
**CC:** GUSTIN, CHRISTOPHE [AG/5040] [/O=MONSANTO/OU=EA-5041-01/CN=RECIPIENTS/CN=83930]  
**Subject:** TAC data and the GTF publication on chronic/carc studies

David, Wakimori san,

We need to move on with finalising the chronics paper. Is the TAC situation possible to resolve in the near future? From the notes below it looks likely not to be. However, from an EU perspective we need to get the chronics paper published. Can we go ahead based on the data available from the GTF companies and add TAC as an addendum at some time in the future if access becomes possible?

What do you think?

Regards

Richard

- TAC now accepts Final Draft PWG Report on the kidney slides from TAC's 2 year rat study received from St.Louis.

In response to our request to share the full report of mouse carcinogenicity study conducted with TAC's material in order for us to include TAC's data in the publication on glyphosate and cancer risk, TAC

declined based on the lack of consensus among TAC members since FSC review is still underway and the original mouse data suggested some carcinogenic potential which was denied in the process of FSC

review.

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19 *Co-Lead Counsel for Plaintiffs*  
20 *in MDL No. 2741*

21 UNITED STATES DISTRICT COURT  
22 NORTHERN DISTRICT OF CALIFORNIA

23 IN RE: ROUNDUP PRODUCTS  
24 LIABILITY LITIGATION

MDL No. 2741  
Case No. 16-md-02741-VC

Hearing: February 27, 2017, 9:30 a.m.

25 This document relates to all cases

Courtroom 4, 17h Floor, N.D. Cal.

San Francisco, CA

26 **PLAINTIFFS' SUBMISSION IN RESPONSE TO PRETRIAL ORDER NO. 8**

1 As a preliminary matter, it is important for the Court to understand that the IARC and the  
2 EPA are analyzing different issues. Aside from issues of methodology, the fundamental  
3 difference between their assessments is that IARC performs a “hazard assessment”—can  
4 glyphosate and/or Roundup<sup>®</sup> cause NHL—while EPA makes a “risk assessment”—at what level  
5 is there a risk of cancer and is that an acceptable risk. In addition, IARC considers studies of  
6 both glyphosate and the formulated product while the EPA considers only glyphosate. In a legal  
7 sense, IARC performs a general causation assessment.

9 IARC is the “gold standard” for scientific cancer assessments and followed generally  
10 accepted and sound methodology in reaching its conclusion that glyphosate is a probable human  
11 carcinogen;<sup>1</sup> thus, its conclusions are reliable and relevant to a general causation analysis. The  
12 President’s Cancer Panel, Reducing Environmental Cancer Risk, at 13 (Apr. 2010), *available at*  
13 [http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP\\_Report\\_08-09\\_508.pdf](http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf).  
14 There is no evidence of IARC bias. The Federal Judicial Center lists IARC as one “of the most  
15 well-respected and prestigious scientific bodies” and states that when IARC Monographs are  
16 available, they are “generally recognized as authoritative.” *See* Reference Manual On Scientific  
17 Evidence, 3rd Edition (2011) (Reference Manual), pp. 20, 564.

20 On the other hand, because the EPA does not actually review the carcinogenicity of the  
21 Roundup<sup>®</sup> formulation and because there are substantial flaws and biases in its procedures and  
22 methods to determine whether glyphosate can cause non-Hodgkin lymphoma (“NHL”), EPA’s  
23 *ad hoc* conclusions are neither reliable nor relevant to support issues of general causation.  
24

---

26 <sup>1</sup> World Health Org., IARC Monographs on the Evaluation of Carcinogenic Risks to  
27 Humans: Some Organophosphate Insecticides and Herbicides (Volume 112) (hereinafter  
28 “Monograph”), *available at* <http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-10.pdf>.

1           **I.       IARC IS RELEVANT TO GENERAL CAUSATION**

2           **A.       IARC: The Gold Standard for Scientific Cancer Assessments**

3           The International Agency for Research on Cancer (IARC) is the most preeminent cancer-  
 4 assessment authority in the world.<sup>2</sup> As such, the IARC monographs should be reviewed,  
 5 considered, and relied upon by all causation experts in this litigation, whether for Plaintiffs or  
 6 Monsanto. *See Estate of Barabin v. AstenJohnson, Inc.*, 740 F.3d 457, 463 (9th Cir. 2014)  
 7 (considering whether “theory or technique enjoys general acceptance within the relevant  
 8 scientific community” in addressing *Daubert*’s reliability prong). “The IARC Monographs are ...  
 9 relevant to a determination of general causation and [are] the type of scientific data relied on by  
 10 experts in the field of study.” *Lewis v. Airco, Inc.*, No. A-3509-08T3, 2011 WL 2731880, at \*18  
 11 (N.J. Super. Ct. App. Div. July 15, 2011).  
 12  
 13

14           In assessing cancer etiology, scientists utilize a hierarchy of evidence to review the  
 15 scientific literature. *See Oxford Centre for Evidence Based Medicine – Levels of Evidence.*<sup>3</sup> At  
 16 the top of that hierarchy are systematic reviews, which “focus on peer-reviewed publications  
 17 about a specific health problem and use rigorous, standardized methods for selecting and  
 18 assessing articles.” *Id.* (glossary); *see also Federal Judicial Center, Reference Manual on*  
 19 *Scientific Evidence 723-24* (“When ordered from strongest to weakest, systematic review of  
 20 randomized trials (meta-analysis) is at the top, followed by single randomized trials, systematic  
 21

22  
 23           <sup>2</sup> The United Nations World Health Organization founded IARC in 1965 “to promote  
 24 international collaboration in cancer research.” IARC’s Statute, Rules, and Regulations,  
 25 Fourteenth Edition (IARC Statute), Art. I, at 5-6, (Ex. 1, excerpts from IARC statute.) The  
 26 United States was a founding member of IARC and, as of the date of this memorandum, remains  
 27 a member. *Id.* at 5, 27 (Ex. 1). Each IARC member state nominates scientific experts to  
 28 comprise IARC’s Scientific Council, the body that reviews IARC’s cancer research program. *Id.*  
 at 8. Further, members elect representatives to serve on the Governing Council, which is  
 responsible for, *inter alia*, setting general policy for IARC. *Id.* at 7.

<sup>3</sup> <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>.

1 reviews of observational studies, single observational studies, physiological studies, and  
2 unsystematic clinical observations.”).<sup>4</sup> As the Court has noted, the experts will review the  
3 underlying studies that IARC relied on as part of its assessment. Nonetheless, independent  
4 systematic reviews such as those conducted by IARC are strong evidence upon which experts in  
5 the field rely, and thus, experts in this litigation may also appropriately rely in part on IARC.  
6  
7 Fed. R. Evid. 703.

8 In assessing whether Roundup<sup>®</sup> can cause NHL, evidence-based science dictates that  
9 experts review the most reliable systematic review of cancer etiology, the IARC Monograph. In  
10 making cancer assessments, IARC considers all relevant, publicly available scientific evidence to  
11 determine whether a particular chemical or agent causes cancer.<sup>5</sup> See Reference Manual on  
12 Scientific Evidence, 3<sup>rd</sup> Edition (2011) (Reference Manual) at 20. Indeed, the Reference Manual  
13 describes IARC’s cancer assessments as follows:  
14

15 IARC, a well-regarded international public health agency,  
16 evaluates the human carcinogenicity of various agents. In doing so,  
17 IARC obtains all of the relevant evidence, including animal studies  
18 as well as any human studies. On the basis of a synthesis and  
19 evaluation of that evidence, IARC publishes a monograph  
20 containing that evidence and its analysis of the evidence and  
21 provides a categorical assessment of the likelihood the agent is  
22 carcinogenic. . . . ***When IARC monographs are available, they are  
generally recognized as authoritative. Unfortunately, IARC has  
conducted evaluations of only a fraction of potentially  
carcinogenic agents, and many suspected toxic agents cause  
effects other than cancer.***

23  
24  
25  
26 <sup>4</sup> Monograph, at 350 (citing meta-analysis showing a statistically significant increase in  
27 NHL).

28 <sup>5</sup> In contrast, in its registration analysis of glyphosate, the EPA mostly considered private,  
non-peer-reviewed studies and literature funded and/or conducted by Monsanto.

1 Reference Manual at n. 46 (emphasis added). The American Cancer Society also relies  
 2 on IARC for its list of substances that are known or suspected to cause cancer.<sup>6</sup> The U.S.,  
 3 Department of Health and Human Services considers IARC monographs to be “critical  
 4 references that inform health policy and cancer research worldwide about carcinogenic risks to  
 5 reduce cancer globally.” Limited Competition, IARC Monographs Program (2014).<sup>7</sup>  
 6

7 Because of its exacting standards and neutrality, federal laws incorporate IARC  
 8 classifications into regulatory standards.<sup>8</sup> Similarly, many California state laws<sup>9</sup> and other  
 9 states’ laws<sup>10</sup> specifically rely on IARC’s cancer assessments. Importantly, when the State of  
 10

11 <sup>6</sup> [https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-](https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html)  
 12 [carcinogens.html](https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html).

13 <sup>7</sup> [https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-503.html# Part 2. Full](https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-503.html#_Part_2_Full)

14 <sup>8</sup> For example, under the Toxic Substances Control Act of 1976 (TSCA), as interpreted  
 15 by the EPA, “[a] chemical is considered to be a known or potential human carcinogen, for  
 16 purposes of TSCA section 12(b) export notification, if that chemical is . . . classified as . . .  
 17 ‘probably carcinogenic to humans’ (Group 2A) . . . by the World Health Organization  
 18 International Agency for Research on Cancer (IARC)[.]” 40 C.F.R. § 707.60(2)(c). Similarly,  
 19 the U.S. Consumer Product Safety Commission (CPSC) and the Occupational Safety and Health  
 20 Administration (OSHA) both recognize and accept the authority of IARC in assessing the  
 21 potential cancer hazard of an agent. *See* 16 C.F.R. § 1500.135(a)(1)-(3) (relying on the IARC  
 22 classifications for known, probable and possible human carcinogen assessments); 29 C.F.R. §  
 23 1910.1450(b) (defining carcinogen as any substance identified as such by IARC). The U.S.  
 24 Centers for Disease Control and Prevention lists IARC Monographs as one of the “Other  
 25 Government Agency Resources” for identifying chronic health effects of exposure to hazardous  
 26 chemicals. *See* <http://www.cdc.gov/niosh/topics/chemical-safety4other>.

27 <sup>9</sup> California’s Carcinogen Identification Committee deems IARC an authoritative body  
 28 for purposes of Proposition 65’s listing mechanism. *See* 27CCR, § 25306, subd. (m)(1).  
 California’s Labor Code, which provides workers information about hazardous chemicals in the  
 workplace, requires OEHHA to list “substances identified by reference in Labor Code Section  
 6382(b)(1)”, which, in turn, identifies “[s]ubstances listed as human or animal carcinogens by the  
 [IARC].” 27CCR, § 25249.8, subd. (a) and (b)(1).

<sup>10</sup> Other states also rely on IARC’s carcinogenicity evaluations. Pennsylvania’s  
 hazardous substance list must include all substances listed by IARC as having “sufficient  
 evidence of carcinogenicity in animals.” (Penn. Statutes, tit. 35, § 7303, subd. (a)(6); Penn.  
 Admin. Code, tit. 34, § 323.5, subd. (20)(6)). New Jersey’s “Right to Know Hazardous  
 Substance List” must be updated based on the IARC Monograph Supplements. (N.J. Admin.  
 Code, tit. 8:59-93, subd. (b)(7)). Rhode Island is required by statute to maintain a hazardous  
 and/or toxic chemical list that includes chemicals listed as carcinogens by IARC (R.I. Gen.

1 California noticed its intent to list glyphosate as a chemical “known to cause cancer,” which  
2 requires Monsanto to warn Californians about the dangers of glyphosate,<sup>11</sup> Monsanto sued  
3 California in Fresno Superior Court to avoid providing cancer risk warnings. At present, the  
4 Court has issued a tentative ruling only.

5  
6 **B. IARC’s Assessment Process**

7 Each IARC assessment is published in the form of a “Monograph,” which comprises a  
8 Preamble (*see IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*,  
9 Preamble, 2006, Ex. 2) (hereinafter “Preamble”) and “critical reviews and evaluations of  
10 evidence of the carcinogenicity of a wide range of human exposures.” *Id.* at 2. Monographs are  
11 “used by national and international authorities to make risk assessments, formulate decisions  
12 concerning preventive measures, provide effective cancer control programmes and decide among  
13 alternate options for public health decisions.” *Id.* at 3.<sup>12</sup> IARC’s assessment process is a year-  
14 long endeavor, described in detail in the Preamble, which involves a review of peer-reviewed  
15 scientific literature and data from publicly-available government agency reports. *Id.* at 4.

16  
17  
18 The Working Group evaluating glyphosate included 17 experts from around the world,  
19 who volunteered their time to undertake this important public health assessment. These experts  
20

21  
22 Laws, tit. 28, § 28-21-2(13)). Massachusetts’ list of toxic or hazardous substances includes  
23 substances found to have sufficient evidence of carcinogenicity in animals as indicated in the  
24 IARC Monographs. (Mass. Reg, tit. 105, § 670.010, subd. (B)(1); Mass. Gen. Laws Ann. 111F §  
25 4, subd. (b)(2).) These and other states, including Alaska, Connecticut, Illinois, Indiana,  
26 Louisiana, Missouri, Nevada, New Hampshire, Oregon, Tennessee, Texas, Vermont, Virginia,  
27 and Washington, rely on IARC's evaluations to help them identify carcinogens for public health  
28 purposes. A list of these state statutes is attached as Exhibit 3.

<sup>11</sup> <http://oehha.ca.gov/proposition-65/crn/notice-intent-list-tetrachlorvinphos-parathion-malathion-glyphosate>

<sup>12</sup> While the Preamble uses the term “risk,” IARC Monographs evaluated cancer “hazards,” not risk. Preamble, at 2-3.

1 included scientists from the U.S. EPA, California EPA, and the National Cancer Institute.<sup>13</sup>  
2 IARC also permits representatives from government agencies and even observers from affected  
3 industries to observe the meeting. *Id.* For example, Monsanto retained Thomas Sorahan to  
4 attend the meeting for Monograph 112 on Monsanto's behalf; he reported that the Chair, sub-  
5 chairs, and invited experts for the glyphosate Working Group were "very friendly" and "prepared  
6 to respond to all comments I made." He continued, "[i]n my opinion the meeting followed the  
7 IARC guidelines." Ex. 4, MONGLY00977035-36.

8  
9 The product of this process is the IARC Monograph, which includes exposure data,  
10 studies of cancer in humans, studies of cancer in experimental animals, mechanistic and other  
11 relevant data, a summary of the contents, and an evaluation and rationale for the chemical's  
12 categorization. As detailed in the Preamble, IARC's classification process is rigorous and  
13 includes numerous procedures and safeguards designed to promote the scientific integrity of its  
14 decisions. *See AFL-CIO v. Deukmejian*, 212 Cal.App.3d 425, 433 (1989). Scholars agree that  
15 the IARC review process follows well-accepted and sound methodology, including interpreting  
16 data according to the generally accepted Bradford Hill criteria for cancer assessments. *See IARC*  
17 *Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans*, Pearce, *et al.*,  
18 *Environmental Perspectives*, Vol. 123, No. 6, at 513 (June 2015), at 6.

19  
20  
21 Monsanto is well aware of the significance of a finding of carcinogenicity by IARC.  
22 After learning that IARC planned to assess glyphosate, it launched a campaign to discredit an  
23 IARC finding, even before the Working Group meeting began.<sup>14</sup> In a PowerPoint designed to  
24 confront IARC's anticipated assessment of carcinogenicity, Monsanto describes IARC as an  
25

26  
27 <sup>13</sup> <http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-F03.pdf>.

28 <sup>14</sup> *See* Ex. 5, in which Monsanto laid out in a Power Point presentation the respect the scientific community and governments around the globe have for IARC assessments.

1 agency that “promote[s] international collaboration in cancer research” and “[i]dentifies agents  
2 that increase risk of human cancer.” *Id.* at Slide 2. Monsanto understood that because of  
3 IARC’s reputation, a finding of carcinogenicity would “disrupt our narrative,” and “call into  
4 question the safety of glyphosate/Roundup, putting industry on the defensive.” *Id.* at Slide 6.<sup>15</sup>  
5  
6 In reaction to IARC’s determination that glyphosate is a probable carcinogen, Monsanto has  
7 engaged in an aggressive media and political attack on IARC generally and the Monograph 112  
8 members specifically, an unprecedented reaction in the cancer agency’s 40-year history of  
9 reviewing carcinogens.

### 10 **C. Judicial and Industry Reliance on IARC**

11 Federal courts, which have relied on its methodology and classifications, routinely  
12 acknowledge IARC’s status as an expert scientific agency. *See, e.g., Adams v. Cooper Industries*  
13 (E.D. Ky. Apr. 4, 2007, No. 03-476-JBC) 2007 WL 1075647, at \*14 (holding that IARC  
14 classifications were admissible, as they were probative, not unduly prejudicial, and “result from  
15 an in-depth analysis by experts in their fields”); *Current v. Atochem* (W.D. Tex. Nov. 30, 2001,  
16 No. W-00-CA-332) 2001 WL 36101283, at \*4 (using IARC’s findings as a benchmark for  
17 evaluating expert testimony for link between rectal cancer and arsenic); *Burst v. Shell Oil Co.*,  
18 No. CIV.A. 14-109, 2015 WL 3620111, at \*8 (E.D. La. May 9, 2015), *aff’d*, 650 F. App’x 170  
19 (5th Cir. 2016), *cert. denied*, 137 S. Ct. 312, 196 L. Ed. 2d 219 (2016); *Baldonado v. Wyeth*  
20 (N.D. Ill. Aug. 31, 2012, No. 04 C 4312), 2012 WL 3779100, at \*4-6). Even Monsanto has relied  
21 on IARC’s published monographs to argue that certain chemicals should not be considered  
22  
23  
24

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25 <sup>15</sup> Monsanto has spoken favorably about IARC’s methodology in court filings in other  
26 cases as well. In *Town of Lexington v. Pharmacia, et al.*, C.A. No. 12-CV-11645, Rec. Doc.  
27 263, for example, a case involving harm caused by polychlorinated biphenyls (PCBs), Monsanto  
28 took the position that IARC’s methodology was sound and that its expert followed a similar  
methodology, albeit reaching a different conclusion. *See Ex. 6 at 6-8.*

1 carcinogens. *See, e.g., Williams v. Monsanto Co.* (E.D. La. Feb. 20, 1997, No. 93-4237) 1997  
2 WL 73565, \*2 (granting summary judgment for defendant in part because, as defendant argued,  
3 the chemical had not been classified as a human carcinogen by IARC).<sup>16</sup> In short, IARC is a key  
4 piece of the general causation analysis.

## 6 **II. EPA’S ACTIONS ARE FLAWED, BIASED, AND IRRELEVANT TO 7 GENERAL CAUSATION**

### 8 **A. EPA Does Not Review The Carcinogenicity of Roundup<sup>®</sup>**

9 The EPA’s role is not to assess the carcinogenicity of Roundup<sup>®</sup>; rather, it is to “register”  
10 glyphosate for sale as a pesticide. Pesticide registration is an administrative procedure that  
11 includes examination of the ingredients of a pesticide, geographic use, frequency of use, and  
12 storage and disposal practices for a pesticide pre-and-post use. 40 C.F.R §§150-189. FFDCA  
13 and FIFRA were amended in 1996 by the Food Quality Protection Act of 1996 (FQPA), 21  
14 U.S.C. § 301 *et seq.*, which vests power in the EPA’s Office of Pesticide Protection (OPP) to  
15 evaluate the risks associated with the use of pesticides to make safety determinations. Unlike  
16 IARC, the scientific data and studies that EPA considers pursuant to FIFRA are provided by the  
17 companies seeking registration. *See* 40 C.F.R. §160. There is no requirement that reports and  
18 studies be subject to peer review or free from bias or influence, and often (as the case here) they  
19 are not.  
20  
21

22 EPA’s minimal standards do not require human health data submissions related to the  
23 formulated product—here, Roundup<sup>®</sup>. Instead, EPA regulations require only studies and data  
24

---

25 <sup>16</sup> Although not directly on point and based on facts different than those here, the Fifth  
26 Circuit Court of Appeals mentioned IARC’s “weight of the evidence” standard in the context of  
27 assessing reliability required for admission of expert opinions in two cases, expressing  
28 disapproval of an expert’s *sole* reliance upon others’ research. *See, e.g., Johnson v. Arkema, Inc.*, 685 F.3d 452, 464 (5th Cir. 2012); *Allen v. Pennsylvania Eng’g Corp.*, 102 F.3d 194, 198 (5th Cir. 1996).

1 that relate to the active ingredient, which in the case of Roundup<sup>®</sup> is glyphosate.<sup>17</sup> As a result,  
2 the body of scientific literature EPA has reviewed is not only primarily provided by the industry,  
3 but it also only considers *one part* of the chemical ingredients that make up Roundup<sup>®</sup>. In fact,  
4 Monsanto's lead toxicologist, Dr. Donna Farmer, recognized that Monsanto "cannot say that  
5 Roundup<sup>®</sup> does not cause cancer" because, "[w]e [Monsanto] have not done the carcinogenicity  
6 studies with Roundup<sup>®</sup>." Deposition of Donna Farmer at 49:21-50:8, quoting Ex. 1-8 (Ex. 7  
7 (Donna Farmer deposition excerpts)).<sup>18</sup> Further, as Dr. Farmer explained, in the 35 years that  
8 Roundup<sup>®</sup> has been on the market, Monsanto has conducted no chronic carcinogenicity studies  
9 on the formulated Roundup<sup>®</sup> product because such a study was not required by the EPA for  
10 registration of glyphosate. *Id.* at 51:22-52:12. Simply put, the EPA does not require, and thus  
11 does not consider, chronic effects data resulting from continuous exposure to Roundup<sup>®</sup>—the  
12 root of all Plaintiffs' allegations in this case.<sup>19</sup> For this fact alone, the EPA's conclusions related  
13 to glyphosate should be excluded as irrelevant.

14  
15  
16 **B. EPA's Self-Corrective Attempts Highlight Its Process Gaps**

17 Potentially in an effort to correct the flaws in its pesticide registration analysis, following  
18 IARC's classification of glyphosate as a 2A carcinogen, the EPA delayed re-registration of  
19

20  
21  
22  
23 <sup>17</sup> In 1992, the Health Effects Division (HED) within EPA's OPP determined that  
24 regulation of metabolites in glyphosate need not be regulated based on toxicological  
25 considerations regardless of levels observed in food or feeds. *See*, MONGLY02811704-  
26 2811785 at 2, dated June 2, 2009, (hereinafter, "Scoping Document") (attached as Ex. 8).

27 <sup>18</sup> One of the ingredients in the formulated product is polyethozylated tallow amine  
28 (POEA). Monsanto is being forced to remove POEA from Roundup in the European Union  
(Farmer Dep. at 79:24-82:13).

<sup>19</sup> Furthermore, Monsanto admits that the additives have biological action and are not  
inert in the biological sense; they are only inert in that they have no herbicidal effect. Farmer  
Dep. at 417:19-23.

1 glyphosate (the process began in 2009) and asked Monsanto to submit additional studies.<sup>20</sup>

2 These EPA requests included materials Monsanto did not previously submit to the agency. Most  
3 notably, the EPA specifically requested European cancer data that Monsanto previously  
4 submitted to the German Federal Institute for Risk Assessment (BfR) but not to the EPA.<sup>21</sup> The  
5 EPA has not yet issued a final decision related to the review of these newly obtained materials.  
6

7 On September 12, 2016, OPP submitted an issue paper on the carcinogenic potential of  
8 glyphosate, wherein it issued a “proposed conclusion”: glyphosate is “not likely to be  
9 carcinogenic to humans *at doses relevant to human health risk assessment.*” (emphasis  
10 added).<sup>22</sup> There are no authors listed on this issue paper.<sup>23</sup> This draft report reiterates and  
11 adopts the conclusions of an October 2015 assessment by Jess Rowland of the OPP’s Cancer  
12 Assessment Review Committee (“CARC”).<sup>24</sup> In arriving at this not yet peer-reviewed decision,  
13 the OPP explicitly noted that its review “focused on studies on the active ingredient glyphosate”  
14 and “additional research could also be performed to determine whether formulation components,  
15 such as surfactants, influence the toxicity of glyphosate formulations.”<sup>25</sup> The OPP noted that it  
16  
17

18 <sup>20</sup> See attached Ex. 9. MONGLY02054538-40, email between Monsanto and EPA,  
19 3/31/2016 (initial study request); *also see*, MONGLY03416927, email between Monsanto and  
20 EPA, 5/17/2016 (request for second list of studies).

21 <sup>21</sup> See attached Ex. 10. MONGLY03410604 at 3410607, email between Monsanto and  
22 EPA, 5/23/2016 (following up on an oral conversation related to the EPA’s request for European  
23 cancer data for glyphosate).

24 <sup>22</sup> This statement shows that EPA is not considering whether glyphosate causes NHL;  
25 rather, it addresses the dosage required to develop NHL.

26 <sup>23</sup> The OPP assessment is not yet final. The issue paper and proposed conclusion was  
27 supposed to be submitted for peer review in October 2016, but that assessment was then  
28 postponed to December 2016. From December 13 to 16, 2016, the EPA held FIFRA Scientific  
Advisor Panel (“SAP”) meetings to consider issues raised by the OPP’s evaluation of glyphosate  
but no final report has yet issued.

<sup>24</sup> CARC also limits its conclusion to the amount of pesticide required to cause NHL; it  
also does not address the “general causation” question of whether Roundup<sup>®</sup> can cause NHL at  
any level.

<sup>25</sup> OPP draft assessment, at 141.

1 rejected all studies that considered Roundup<sup>®</sup>—the formulated product—instead of studies that  
2 isolated glyphosate because “[g]lyphosate formulations contain various components other than  
3 glyphosate and it has been hypothesized these components are more toxic than glyphosate  
4 alone.”<sup>26</sup> In its charge to the FIFRA Scientific Advisory Panel (“SAP”), established to perform a  
5 peer review of the OPP draft assessment, the OPP notes that “[a]lthough there are studies  
6 available on glyphosate-based pesticide formulations, the agency is soliciting advice from the  
7 SAP on this evaluation of human carcinogenic potential for the active ingredient glyphosate only  
8 at this time.”<sup>27</sup> The SAP is still considering the evidence on glyphosate and has not issued any  
9 findings to date. Because Plaintiffs here allege exposure to Roundup<sup>®</sup>, the OPP review (even if  
10 it were free of irregularities identified below) is not relevant to this litigation.  
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13 In stark contrast, IARC’s review of glyphosate included data relating to the manner in  
14 which it is used in the real world—as one of the ingredients of the Roundup<sup>®</sup> formulation—and  
15 furthermore, necessarily included “high dose” and “injected” studies because these are studies  
16 that can determine the carcinogenic potential of both glyphosate and Roundup<sup>®</sup>.  
17

### 18 C. EPAs “Cancer Risk Assessment” for Glyphosate Is Flawed

19 The EPA’s own cancer risk guidelines describe the meta-analysis technique used by  
20 IARC and acknowledge that:

21 Meta-analysis is a means of integrating the results of multiple  
22 studies of similar health effects and risk factors. This technique is  
23 particularly useful when various studies yield varying degrees of  
24 risk or even conflicting associations (negative and positive). It is  
25 intended to introduce consistency and comprehensiveness into  
what otherwise might be a more subjective review of the literature.

26 <sup>26</sup> *Id.* at 70.

27 <sup>27</sup> EPA, Glyphosate: Evaluation of Carcinogenic Potential, Charge to the FIFRA SAP for  
28 October 18-21, 2016 Meeting [https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate\\_sap\\_charge\\_questions\\_-final.pdf](https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_sap_charge_questions_-final.pdf) (last accessed February 3, 2017).

1 The value of such an analysis is dependent upon a systematic  
2 review of the literature that uses transparent criteria of inclusion  
and exclusion.<sup>28</sup>

3 IARC “conducted an objective statistical analysis of the results of all of the available  
4 studies on glyphosate and non-Hodgkin lymphoma, which included the AHS and all of the case-  
5 control studies. The data from all of the studies combined show a statistically significant  
6 association between non-Hodgkin lymphoma and exposure to glyphosate.”<sup>29</sup> The EPA provides  
7 no criticism of the meta-analysis itself or its application by IARC. There is no demonstrated bias  
8 or demonstrated confounding factor—only the potential that these exist. Despite IARC’s  
9 systematic review ranking at the top of the hierarchy of evidence relied upon by experts in the  
10 field and in the EPA’s own guidelines, Jess Rowland of the OPP simply ignored it. Still, the  
11 CARC did not look at the primary literature related to glyphosate. True to history, CARC based  
12 its review upon industry-sponsored articles and studies. CARC compounded this error by  
13 ignoring relevant studies so as to only examine risk analysis, not hazard analysis, i.e., the general  
14 causation issue.  
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18 EPA’s carcinogenicity review of glyphosate relied heavily on Greim, et al. (2015),  
19 Williams (2000) and Kier & Kirkland (2013).<sup>30</sup> EPA Memorandum, GLYPHOSATE: Report of  
20 the Cancer Assessment Review Committee, October 1, 2015 at 8; EPA Issue Paper, September  
21

22 <sup>28</sup> U.S. EPA, Guidelines for Carcinogen Risk Assessment, available at,  
[https://www.epa.gov/sites/production/files/2013-09/documents/cancer\\_guidelines\\_final\\_3-25-05.pdf](https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf).

23 <sup>29</sup> [https://www.iarc.fr/en/media-centre/iarcnews/pdf/Q&A\\_Glyphosate.pdf](https://www.iarc.fr/en/media-centre/iarcnews/pdf/Q&A_Glyphosate.pdf).

24 <sup>30</sup> Greim, et al. (2015), Evaluation of carcinogenic potential of the herbicide glyphosate,  
25 drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies, *available*  
26 *at* <http://www.tandfonline.com/doi/full/10.3109/10408444.2014.1003423>; Kier & Kirkland  
27 (2013), Review of genotoxicity studies of glyphosate and glyphosate-based formulations,  
*available at* <http://www.tandfonline.com/doi/full/10.3109/10408444.2013.770820>; Williams  
28 (2000), Safety Evaluation and Risk Assessment of the Herbicide Roundup1 and Its Active  
Ingredient, Glyphosate, for Humans, *available at*  
<http://www.msaf.gob.ar/agroquimicos/pdf/Williams-et-al-2000.pdf>.

1 2016, at 22. The Greim article, co-authored by a Monsanto employee, offers Monsanto's  
2 opinions related to thirteen industry animal studies that have not been subjected to the peer-  
3 review process, and was newly submitted to the Agency as part of OPP's current review of  
4 glyphosate. Importantly, the Greim article does not include sufficient underlying data to support  
5 the conclusion; as a result, the article was not, and could not have been, considered by IARC.  
6 IARC evaluates review articles to determine whether the authors provide sufficient information  
7 about the data reviewed in order to arrive at their conclusion; if they do not, then IARC does not  
8 consider it because it cannot perform an independent analysis. Preamble at 18.  
9

10 The importance of IARC's review, and alternatively EPA's flawed review, is highlighted  
11 by the fact that Monsanto's Toxicology Manager, David Saltmiras, was a ghost-writer on the  
12 Kier & Kirkland publication and Bill Heydens, Saltmiras's boss, was a ghostwriter on the  
13 Williams (2000) article.<sup>31</sup> The EPA may be unaware of Monsanto's deceptive authorship  
14 practice and therefore accepted representations about 17 genotox studies reported in the Kier &  
15 Kirkland article without having looked at the original reports. See EPA Position Paper,  
16 September 2016, page 8. In the Greim paper, at least one study was omitted from the manuscript  
17 (and thus omitted from the EPA review) because "the original mouse data suggested some  
18 carcinogenic potential." Ex. 13, MONGLY01009950. Therefore, Monsanto's corporate  
19 practices have long controlled the literature.  
20  
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22 **D. There is Disagreement within EPA Whether the OPP Assessment is Valid**  
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25 <sup>31</sup> See attached Ex. 11, MONGLY02145917, (Saltmiras removed as author in part and  
26 non-Monsanto employee David Kirkland added because "manuscript turned into such a large  
27 mess of studies reporting genotoxic effects, that the story as written stretched the limits of  
28 credibility among less sophisticated audiences."); Ex. 12, MONGLY00977264 ("we would be  
keeping the cost down by us doing the writing and they would just edit & sign their names so to  
speak. Recall that is how we handled Williams Kroes & Munro, 2000.").

1           There is no clear consensus on the glyphosate analysis even within the EPA. Recently  
2 published internal documents obtained in a Freedom of Information (FOIA) request filed by The  
3 Free Market Environmental Law Clinic<sup>32</sup> reveal that when the EPA's Office of Research and  
4 Development (ORD) scientists reviewed and commented on OPP's glyphosate cancer analysis,  
5 ORD scientists *agreed* with IARC that "'a positive association has been observed' for which a  
6 causal association is Credible, but chance, bias, or confounding could not be ruled out with  
7 reasonable confidence." *See* Office of Research and Development, Summary of Comments on  
8 OPP's glyphosate cancer assessment (December 14, 2015), attached here as Exhibit 14.  
9

10           The ORD reviewers also noted that "the analysis of the cancer data in the [OPP]  
11 assessment was basically conducted on a study-by-study basis instead of using a more inclusive,  
12 systematic approach to provide an integrated analysis of the data." The authors of the Reference  
13 Manual of Scientific Evidence call this technique "atomization," and in disapproving this  
14 "slicing and dicing" approach state that:  
15

16                       scientific inference typically requires consideration of numerous  
17 findings, which, when considered alone, may not individually  
18 prove the contention. It appears that many of the most well-  
19 respected and prestigious scientific bodies (such as the  
20 International Agency for Research on Cancer (IARC), the Institute  
21 of Medicine, the National Research Council, and the National  
22 Institute for Environmental Health Sciences) consider all the  
relevant available scientific evidence, taken as a whole, to  
determine which conclusion or hypothesis regarding a causal claim  
is best supported by the body of evidence.

23 *Id.* at 20.

24           It is vitally important that all conflicts of interest and bias be eliminated where possible.  
25 "[M]ethodology that is 'biased toward a particular conclusion' ... does not 'comport[ ] with the  
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28 <sup>32</sup> These documents are available on the FOIA website:  
<https://foiaonline.regulations.gov/foia/action/public/view/request?objectId=090004d280e576c0>.

1 dictates of good science.” *Perez v. State Farm Mut. Auto. Ins. Co.*, No. C 06-01962 JW, 2012  
2 WL 3116355, at \*6 (N.D. Cal. July 31, 2012) (quoting *Daubert v. Merrell Dow Pharms., Inc.*, 43  
3 F.3d 1311, 1320 (9th Cir.1995). EPA is plagued with bias. As Plaintiffs have already briefed in  
4 the motion to compel the deposition of Jess Rowland, EPA employees are unduly influenced by  
5 Monsanto. Plaintiffs herein incorporate that brief by reference, as well as the opposition to seal  
6 the documents to that brief.<sup>33</sup> Specifically, Plaintiffs seek the deposition of Jessie Rowland as  
7 the former head of the CARC as the core piece of discovery to evaluate the EPA’s inherent flaws  
8 and biases. Similarly, the parties have agreed to, and are in the process of scheduling, the  
9 deposition of Dr. Aaron Blair (Overall Chair of the IARC Working Group assessing Glyphosate  
10 and Scientist Emeritus at the National Cancer Institute) where the parties will be free to explore  
11 the scientific process that resulted in the IARC monograph on glyphosate.  
12

#### 14 **CONCLUSION**

15 For the reasons stated above, Plaintiffs respectfully submit that IARC’s methods, studies,  
16 reports and conclusions are relevant to general causation, but methods, studies, reports and  
17 conclusions of the EPA are not relevant to general causation.  
18

19 DATED: February 8, 2017

Respectfully submitted,

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<sup>33</sup> However, if the Court allows Monsanto’s experts to rely in whole or in part on EPA conclusions, Plaintiffs should be allowed to conduct discovery on these flawed assessments.

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**Summary of ORD comments on OPP's glyphosate cancer assessment**  
**December 14, 2015**

1. ORD scientists have reviewed OPP's glyphosate cancer analysis and selection of cancer descriptor. The reviewers included two epidemiologists, a pathologist, and several scientists with significant expertise in cancer risk assessment. With the exception of one reviewer who participated in the recent IARC review and two reviewers who participated in the CARC review, an in-depth review of the original literature was not undertaken.
2. The goal of this focused, expedited review was to consider the characterization of glyphosate as "not likely to be carcinogenic to humans," given IARC's recent decision and looking at the totality of the available cancer database.
3. There are several epidemiological studies that vary in quality and study design. For many of the epidemiological studies, it appears that the small sample sizes limit their power to detect an outcome other than the null hypothesis. There are some epidemiological studies that show non-statistically significant elevated risks. One meta-analysis brings together those studies to strengthen the analysis and finds slightly elevated risks. The overall conclusion from IARC is that there is limited evidence of an association between glyphosate and non-Hodgkin's lymphoma (NHL). One major point is that a determination of causality is not what one would expect from most of the studies that are available given their design and power.

ORD's epidemiologists agree with IARC that there is "limited evidence" of carcinogenicity in humans and understand IARC's definition of "limited evidence" as "a positive association has been observed" for which a causal association is "credible, but chance, bias, or confounding could not be ruled out with reasonable confidence [IARC Preamble, section B6]." OPP preferred to dichotomize the epidemiological evidence to be either "causal" or "not causal." This dichotomization appears to be the major factor in the different positions between OPP and IARC with regard to the epidemiological data.

Frameworks for data analysis and causal determinations that are currently in use by EPA and the risk assessment community include gradations of causality. EPA's Cancer Guidelines utilizes these gradations to inform cancer descriptor choices. An example of situation where a less than causal determination is used is for the descriptor "likely to be carcinogenic to humans" – an agent demonstrating a plausible (but not causal) association between human exposure and cancer. The OPP draft risk assessment does not appear to follow these approaches. It would appear that OPP's use of a "yes/no" approach would only lead to cancer descriptors of "carcinogenic to humans" or "not likely to be carcinogenic to humans."

4. Glyphosate has been tested in a large number of 2-year rat and mice studies, including several studies conducted in the same strains. A wide range of tumors have been observed in these studies, including adenomas and some carcinomas. Tumors have been observed in thyroid, liver, skin, pancreas, hemangiosarcoma, lymph, testes, mammary glands, kidney and lung. However, the tumor incidences were generally not statistically significant in pair-wise comparisons and were generally within the range of historical controls. Most tumor types were only observed in one study despite repeat studies within the same strain and similar doses at or above the limit dose.

The tumors found in more than one study were in the pancreas and liver, and were observed in 2 of 4 studies in Sprague Dawley (SD) rats. A positive trend was found for male combined renal tubule adenomas and carcinomas in one CD-1 mouse study. This tumor is relatively rare in CD-1 mice. A positive trend was also found for hemangiosarcoma in males in another CD-1 mouse study. What makes the database so unusual is the large number of animal bioassays that have been conducted and the variety of types of tumors that have been observed, albeit usually at very low incidences. The OPP evaluation concluded that all of the tumors found were not treatment-related.

OPP (and EFSA) focus on pairwise comparisons (which were generally not significant), while IARC also uses trend tests, which yielded several significant results. In a few cases, OPP reported trend test results that differed from those of IARC but did not report which test they used. EPA's cancer guidelines state that "Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumor incidence. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."

5. The ORD reviewers noted that the analysis of the cancer data in the assessment was basically conducted on a study-by-study basis instead of using a more inclusive, systematic approach to provide an integrated analysis of the data. The cancer database for glyphosate is unusual. It is difficult to predict whether such an approach would yield a different outcome. It would likely be a large undertaking. A thorough evaluation of the mutagenic potential of glyphosate was not included in the assessment and was not conducted as a part of this review. This aspect of the assessment is important because if there is evidence of mutagenic potential or if a mutagenic potential has not been adequately ruled out, then characterization of glyphosate as "not likely to be carcinogenic" could be problematic for this reason alone, given the lack of a high-quality negative epidemiological study.
6. The main issue is whether the characterization of cancer potential for glyphosate as "not likely to be carcinogenic to humans" represents the best evaluation of the data. There are five EPA cancer guideline categories:
  - Carcinogenic to humans
  - Likely to be carcinogenic to humans
  - Suggestive evidence of carcinogenic potential
  - Inadequate information to assess carcinogenic potential
  - Not likely to be carcinogenic to humans

According to the cancer guidelines, characterizing a chemical as either "carcinogenic to humans" or "not likely to be carcinogenic to humans" has a high bar with phrases such as "strong evidence" and "robust data" included in these descriptors. For glyphosate, nobody—including IARC—supports the top category (carcinogenic to humans). The descriptor "not likely to be carcinogenic to humans" is appropriate when "the available data are considered robust for deciding that there is no basis for human hazard concern." Examples include situations where there is "convincing evidence in both humans and animals that the agent is not carcinogenic" or animal evidence is available that "demonstrates a lack of carcinogenic effects in both sexes in well-designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects)."

“Likely to be carcinogenic” means that the “weight of the evidence is adequate to demonstrate carcinogenic potential to humans,” giving as an example “an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments.”

“Suggestive” evidence covers a spectrum of evidence ranging from “a positive cancer result in the only study on an agent to a single positive result in an extensive database that includes negative studies in other species.” In ORD’s experience, chemicals can fall into this category at the low end or the high end of the spectrum.

The descriptor “inadequate information to assess carcinogenic potential” is appropriate when “available data are judged inadequate for the other descriptors,” and for which “additional studies would be expected to provide further insights.” However, examples for when to use this descriptor range significantly from “little or no pertinent information,” conflicting evidence (not to be confused with differing results, where “depending on the WOE, differing results can be considered either suggestive evidence or likely evidence),” to “negative results that are not sufficiently robust for not likely.”

**Summary:** The ORD reviewers have not extensively discussed which descriptor might be most appropriate for glyphosate. In ORD discussions to date, “carcinogenic to humans” is clearly not applicable, and IARC and OPP are in agreement. One might classify glyphosate as “likely” on the basis of experimental data alone, by accepting positive trend tests at two anatomical sites (despite differing results in other studies) or by viewing these tumors (which not everyone accepts) as rare. One level down on the continuum puts you at “suggestive evidence.” For this descriptor, one could argue that the evidence is not strong enough for the “likely” descriptor but it cannot be dismissed. The positive association (i.e., limited evidence) of carcinogenicity in humans could arguably rule out the last cancer category (“not likely to be carcinogenic”). One could also argue that this unusual data set is best suited to the descriptor “inadequate information to assess carcinogenic potential” based on an argument that the results are not sufficiently robust for the descriptor “not likely.”

**ORD Recommendation:** To strengthen OPP’s human health assessment and address the differences in the potential cancer findings, we recommend the following:

- Expand the discussion of the cancer data and subsequent findings to include a detailed and thorough discussion of the rationale that caused OPP to come to a different conclusion than IARC, if not directly noting the IARC findings themselves. Key controversies in how one could evaluate the data should be highlighted to provide transparency in how the Agency is making its determination. OPP could include a discussion of the strengths and weaknesses of choosing one cancer descriptor over the other.
- We understand that OPP plans to take the assessment to the SAP for external peer review. We recommend developing charge questions that will be specific to the cancer findings and ask the panel to address the specific scientific differences that exist between the IARC and OPP cancer determinations. ORD is willing to work with OPP to draft the charge questions, or review them before they are finalized.