

Maisons-Alfort, 3 June 2014

THE DIRECTOR GENERAL

OPINION
of the French Agency for Food, Environmental and
Occupational Health & Safety
on the INSERM collective expert appraisal report
“Pesticides. Health effects”

ANSES undertakes independent and pluralistic scientific expert assessments.

ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.

It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its Opinions are made public.

This Opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 3 June 2014 shall prevail.

On 13 June 2013, ANSES¹ received a formal request from the Directorate-General for Food (DGAL) of the French Ministry of Agriculture, Agro-food and Forestry for an Opinion on a collective expert appraisal report by the French National Institute for Health and Medical Research (INSERM) on the health effects of pesticides, biocides and plant protection products.

1. BACKGROUND AND PURPOSE OF THE REQUEST

INSERM carried out a literature review on the human health effects of exposure to pesticides. Epidemiological or experimental data published in the scientific literature were analysed by the group of experts, and the study was made public during a presentation to the French National Assembly on 13 June 2013. The report² has been available since the end of September 2013 and an electronic version was made accessible to ANSES in November 2013. This work is accompanied by a summary outlining the literature analysis and highlighting the main findings and policy lines, as well as the recommendations.

On 13 June 2013, the Directorate-General for Food sent ANSES a formal request to "analyse the data presented in this report on plant protection active substances and, if necessary, make recommendations concerning the marketing authorisations (MAs) for products containing these active substances, especially those intended for amateurs, in particular glyphosate-based, and to "indicate, in particular, if some of these products should be reserved for application by approved operators".

The vast majority of substances identified by the INSERM report as having a presumed moderate or strong association with the occurrence of health effects are chemicals that are now prohibited,

¹ French Agency for Food, Environmental and Occupational Health & Safety

² INSERM. *Pesticides. Effets sur la santé* ["Pesticides. Health Effects"]. Collective Expertise collection, INSERM, Paris, 2013

belonging to the group of organochlorine insecticides, such as DDT or toxaphene, or insecticides with cholinesterase-inhibiting properties, such as terbufos or propoxur. As the request to Anses is to provide recommendations concerning MAs, only data on active substances for which the INSERM report identified a presumed association³ with one or more diseases and which are authorised⁴ in the European Union were analysed in the context of this request.

2. ORGANISATION OF THE EXPERT APPRAISAL

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise - General Requirements of Competence for Expert Appraisals (May 2003)".

The appraisal was performed by the Regulated Products Department at ANSES, and the Expert Committee (CES) on "Plant protection products: chemical substances and preparations" was consulted on 25 March 2014 and 29 April 2014.

3. PRESENTATION OF THE APPROACH

3.1 Introduction

The approach adopted in this opinion aimed to place data from several different disciplines (experimental toxicology, risk assessment and epidemiology) into perspective. This exercise was made more complex by the fact that for a given active substance, there can be different bodies of data.; *a priori* risk assessment is based on a repertoire of validated experimental tests, bibliographic data and data on exposure under conditions of use; when substances and products are re-assessed for renewal of approval all available surveillance and/or post-approval monitoring data are considered. The INSERM expert appraisal relies on data published in the literature.

In addition, in autumn 2013, EFSA⁵ published a comprehensive review⁶ of the literature on epidemiological studies that have examined the link between pesticide exposure and effects on human health, together with a database of all the epidemiological studies analysed in the study report (available online). This review was also included in ANSES's response to the DGAL's request.

Lastly, other available information was taken into account, notably assessments conducted by other agencies such as the US EPA⁷.

As the formal request made to ANSES concerned an analysis of the data presented in the INSERM expert appraisal report on plant protection active substances, the analysis was conducted from a "substance" perspective in contrast to the INSERM report whose approach addressed health effects.

The analysis of the data from different sources (i.e. European assessment, INSERM expert appraisal report, EFSA literature review) aimed to identify any similarities and differences, and to determine whether further investigations were needed to strengthen health risk assessment

³ According to the rating defined by the group of experts.

⁴ Active substances approved under Regulation (EC) No 1107/2009.

⁵ European Food Safety Authority

⁶ NTZANI EE, CHONDROGIORGIS M, NTRITSOS G, EVANGELOU E, TZOULAKI I, 2013. Literature review on epidemiological studies linking exposure to pesticides and health effects. EFSA supporting publication 2013:EN-497, 159 pp. <http://www.Efsa.europa.eu/en/supporting/pub/497e.htm>

⁷ United States Environmental Protection Agency.

(updated assessments, need for new studies, etc.). Indeed, risk assessment and human health impact assessment must be comprehensive and must take into account all available information and consider its value and limits; it must also be adapted over time to ensure that new information is taken into account.

With this in mind, a comparative survey was conducted on the data from the INSERM expert appraisal report, those from the EFSA literature review, and those available in the dossiers submitted as part of the assessment leading to the approval of substances. For each of the active substances considered, the aim was to establish whether there were:

- differences in terms of inventory of information;
- differences in interpreting the studies;
- issues requiring the risk assessment conclusions to be updated, which may or may not result in a need to revise the MAs for products containing these substances.

3.2 Data sources and characteristics

3.2.1 Regulatory risk assessment, hazard, exposure

Regulation (EC) No 1107/2009⁸ and its implementing regulations on the approval of active substances and the placing on the market of plant protection products, and in particular Regulation (EU) No 546/2011⁹ on the criteria for acceptability of risk, are detailed documents indicating the technical data that dossiers must contain and the methods to be applied to obtain them, and specifying, where appropriate, the threshold values beyond which a risk must be considered unacceptable, or the additional tests needed to refine the assessment. These regulations, supplemented by various guidance documents, enable dossiers to be assessed in a harmonised manner throughout the European Union.

The **active substances** authorised for plant protection in the European Union have therefore undergone an assessment endorsed by all the Member States. The dossiers submitted must include relevant information to characterise the intrinsic properties of the substances and therefore the hazards they pose to humans and the environment. They must include the following information:

- Manufacturing process and physico-chemical properties;
- Validated analytical methods in plants, water, soil, air and foodstuffs of animal origin likely to contain residues of the substance;
- Data on the mechanism of biological action, for at least one intended use;
- Toxicity and metabolism studies in mammals, conducted according to the guidelines of the European Union or the OECD¹⁰ and in accordance with good laboratory practice (GLP), in particular:
 - o metabolism in animals;
 - o acute toxicity by oral, dermal or inhalation route, skin or eye irritation, and delayed skin hypersensitivity;
 - o genotoxicity;
 - o toxicity by repeated short- and long-term oral administration and a carcinogenicity study;
 - o toxicity for reproduction in two generations, and for development.

⁸ Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.

⁹ Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products.

¹⁰ Organisation for Economic Cooperation and Development.

In these studies, many physiological, biochemical and histopathological parameters are monitored and measured in the animals. They are used to study the dose-response relationship, mechanism of toxicological action, reversibility of effects, existence of a threshold for adverse effects, species specificity and the potential for extrapolation of effects to humans.

A No Observed Adverse Effect Level (NOAEL) is established for each study. The NOAEL is defined as the highest dose of a substance that does not cause any adverse effects in animals subjected to experiments.

Based on the results of these studies, toxicological reference doses are calculated:

- The Acceptable Daily Intake (ADI) of a chemical is an estimate of the amount of active substance found in food or drinking water that can be ingested daily over a lifetime without appreciable health risk to the consumer, taking into account all known factors at the time of assessment. It is expressed in milligrams of chemical per kilogram of body weight per day (WHO, 1997).
- The Acute Reference Dose (ARfD) of a chemical is the estimated amount of a substance found in food or drinking water, expressed as a function of body weight, that can be ingested over a brief period, usually during one meal or one day, without appreciable health risk to the consumer, taking into account all known factors at the time of assessment. It is expressed in milligrams of chemical per kilogram of body weight (WHO, 1997).
- The Acceptable Operator Exposure Level (AOEL) is the maximum amount of active substance to which the operator may be exposed daily without adverse effect to his/her health; it is an internal dose that takes into account the different routes of operator exposure, i.e. dermal, respiratory and oral.

The assessment of **plant protection products** concerns the quality and effectiveness of the products, the risks that their use may entail for the operator undertaking the treatment, the worker handling treated plants, the bystander during application and people living near cultivated fields, as well as the risks to the consumer, the environment and wildlife. The application for MA is submitted for one or more intended uses; an intended use is defined by the crop treated and the treatment target (pests, weeds, etc.) associated with conditions of use, stating, in particular, the quantity of product used per hectare and the period and frequency of use.

Dossiers must contain information allowing characterisation of the products: physico-chemical properties (flammability, pH, etc.), active substance and co-formulant concentrations, and information allowing the associated hazards to be determined.

The risk assessment takes into account the hazard that has been determined for the product and the exposure level that has been measured by tests or estimated by models. For each of the requested uses, three main categories of risks are assessed:

- Risks for operators¹¹ or users, workers, bystanders and residents,
- Chronic and acute risk for consumers, adults, toddlers (children aged 13-18 months) and infants, for different diets,
- Risks for the environment and for terrestrial and aquatic organisms.

As part of the assessment conducted for renewal of MAs, data from different surveillance networks (measurements in water, toxicovigilance, etc.) are considered..

¹¹ For the purposes of Regulation (EC) No 1107/2009, the following definitions apply:

- a) 'operators' is understood to mean people who take part in activities related to the application of a plant protection product, such as mixing, loading or application, or related to the cleaning and maintenance of equipment containing a plant protection product. Operators can be professionals or amateurs;
- b) 'workers' is understood to mean people who, in the course of their work, enter an area that had previously been treated with a plant protection product, or handle a crop treated with a plant protection product;
- c) 'bystanders' is understood to mean people who happen to be in an area where a plant protection product is being or has been applied, or in an adjacent area, for a purpose other than to work in the treated area or with the treated product;
- d) 'residents' are understood to mean people who live, work or regularly visit an institution near areas treated with plant protection products, for a purpose other than to work in the treated area or with the treated product.

These results are then examined in relation to the decision criteria (known as "uniform principles") specified in Regulation (EU) No 546/2011, which enable a conclusion to be reached as to whether the assessed risks are acceptable or not.

Furthermore at national level, plant protection products for use by non-professional users must comply with Decree No. 2010/1755¹² and the Ministerial Orders¹³ of 30 December 2010 on the sale of plant protection products to non-professional users and the conditions of sale and in particular the packaging requirements for plant protection products.

3.2.2 INSERM collective expert appraisal report

Epidemiological data

The group of experts from INSERM carried out an inventory and analysis of epidemiological studies available in the literature examining the possible association between pesticide exposure and health outcomes: 8 cancer sites, 3 neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis), cognitive or depressive disorders, effects on reproductive function (fertility, pregnancy and child development) and childhood cancers. These are health outcomes that have been identified in previous studies as potentially related to pesticide exposure.

The method used for the literature search (keywords, databases, study period, etc.) and the criteria selected for assessing the quality of the epidemiological studies are not described in the report.

The environmental and occupational epidemiology studies include cohort studies (prospective or retrospective), case-control studies (retrospective) and cross-sectional studies. The analytical or etiologic epidemiology studies (cohort, case-control studies) examine the association between risk factors¹⁴ and disease. The strength of the association between the factor and the disease is measured by statistical risk estimators: relative risk, odds ratio, etc.

The INSERM group of experts established a hierarchy in the relevance of the studies, placing the meta-analysis at the top, then the systematic review, then the cohort study and finally the case-control study. Based on this hierarchy, a scoring system was defined to assess the strength of the association between exposure and the occurrence of health outcomes from the analysis of the study results; for each disease or pathological condition investigated, this score may vary depending on the quality, type and number of available studies, as for example:

(++): strong presumption: based on the results of a meta-analysis, or several cohort studies or at least one cohort study and two case-control studies, or more than two case-control studies;

(+): moderate presumption: based on the results of a cohort study or a nested case-control study or two case-control studies;

(±): weak presumption: based on the results of one case-control study.

Knowledge about exposure is a key element in environmental and occupational epidemiology to avoid misclassification bias (e.g. subjects classified as exposed when they are not). However, characterising exposure and reconstructing past exposure are highly complex, due to many factors, including:

- The great heterogeneity of agricultural activities: the term "farmer" covers a multitude of professional situations such as arable crops, market gardening and greenhouse crops, or livestock activities associated with the farm generating other risk factors such as exposure to animal viruses, allergens, mould, etc., as well as the status of farmer or of farm employee, the size of the farm, etc.;

¹² Decree No 2010-1755 of 30 December 2010 on the sale of plant protection products to non-professional users and the conditions of sale and use of these products.

¹³ Ministerial Order of 30 December 2010 on packaging requirements for plant protection products for use by non-professional users, and Ministerial Order of 30 December 2010 prohibiting the use of certain plant protection products by non-professional users (Official Journal of the French Republic, 12 February 2011).

¹⁴ Factor F is a risk factor for disease M if exposure to factor F alters the probability of occurrence of disease M.

- Exposure to other chemical substances or mixtures such as diesel exhaust fumes, biocidal products;
- The diversity and evolution of products over time;
- The lack of traceability of product use.

Different methods (direct and indirect) have been developed to assess exposure, such as biological or environmental monitoring data, *ad hoc* questionnaires, job crop matrices, analysis of professional calendars, sales data, land use data, etc. Comparisons between these different tools have been made: thus Blair and Zahm¹⁵ (1993) compared self-reporting on pesticide use by participants with information obtained from distributors and found a concordance of only 59 % for herbicides and insecticides. These various tools can be combined with each other but to date none has been validated as a reference method for estimating exposure.

Moreover, the following should be noted regarding interpretation of the results of epidemiological studies. Control of confounding factors is essential in epidemiological studies. A confounding factor is a variable that is statistically related to the examined risk factor or exposure. Confounding factors affect the estimate of the relationship between exposure and the health outcome. As a result of this confusion, a real link may be overlooked, or conversely a link that does not exist in reality may be suggested.

Biological plausibility: mechanistic data

The observation of a statistically significant association between an exposure and a health outcome does not necessarily mean there is causality. In order to demonstrate a causal link, a number of criteria (Hill criteria) must be examined, such as:

- Strength of the association (risk estimators and their confidence intervals);
- Absence of major bias, taking into account other known risk factors;
- Dose-response relationship;
- Temporality;
- Consistency of the association and reproducibility of study results;
- A change in exposure to the risk factor induces a change in the incidence of the disease;
- Biological plausibility: coherence with pathophysiological data, data from experiments.

A rigorous assessment of biological plausibility relies on an updated review of knowledge, based on experimental data drawn most often from a literature review. As part of this formal request, data from studies conducted to meet regulatory requirements when submitting dossiers also had to be taken into account.

Scientific publications generally aim to present a demonstration to support or disprove a hypothesis. They contain a concise summary of the context of the work, the methods used, the most important results and their interpretation by the authors. Original experimental models and protocols can be used. The peer review attests to the quality of work in terms of its consistency, originality or contributions to the state of knowledge, without, however, systematically verifying all the details (raw data, material and methods, etc.).

Studies provided as part of the procedures for placing products on the market are conducted according to protocols and methods defined in guidelines and in compliance with GLP. For each experiment, all the individual data ("raw" data) are appended to the study report.

Mechanistic studies conducted *in vitro* and *in vivo* are essential to provide arguments in favour of a compatible hypothesis. An analysis of all the data provided by epidemiology and experimental studies, in particular those conducted *in vivo*, ensures that bioavailability and metabolism are better taken into account, which will ultimately consolidate the results.

¹⁵ BLAIR A, ZAHM HS. Patterns of pesticide use among farmers: implication for epidemiologic research. *Epidemiology*, 1993, 4: 55-62

3.2.3 EFSA's literature review of epidemiological studies

In 2012, EFSA commissioned a comprehensive review of all the epidemiological studies published between 1 January 2006 and 30 September 2012, investigating the association between pesticide exposure and the occurrence of any health-related outcomes. Publications reporting series of acute poisonings or clinical cases, biomonitoring studies unrelated to health effects, or studies conducted on animals or human cell systems were not included; only epidemiological studies addressing health effects were selected. A search was also conducted on the term "pesticide" in the database of "grey literature" produced in Europe: no reference was found after 2006. Publications that lacked quantitative data for measuring associations were also excluded.

Cohort studies, case-control studies and cross-sectional studies were included. Each study underwent an assessment of its eligibility based on a method including 12 criteria such as study design, precise description of the inclusion/exclusion criteria, level of detail in describing exposure, robustness in the measurement of exposure, adjustment for potential confounding factors, method of assessment of the health outcome, sample size, etc. Among these 12 criteria, three were related to the degree of precision in the description/measurement of exposure, which may explain why a large number of epidemiological studies were not selected.

A total of 602 publications was selected and analysed; most of the studies were case-control (38 %) and cross-sectional (32 %) studies; cohort studies accounted for 25 % and nested case-control studies for 5 %. Nearly half of these studies were conducted in the Americas and 30 % in Europe. Of these studies, 29 % focused on cancer, 15 % on child health, 11 % on reproductive health, 11 % on neurological diseases, 6 % on endocrine diseases, 4 % on respiratory diseases, and 4 % on neuropsychiatric disorders. From this consolidated bibliographic base, meta-analyses were attempted for major outcomes and for those where a relevant meta-analysis published after 2006 was identified; only two meta-analyses were able to be conducted on childhood leukaemia and Parkinson's disease. This EFSA report is accompanied by a database available online¹⁶.

3.3 Active substances selected

The INSERM expert appraisal report is structured according to a disease-based approach; indeed, the vast majority of epidemiological studies have focused on the occurrence of health outcomes in populations exposed to "pesticides" without distinction, a generic term that in reality encompasses a wide variety of situations. However, some epidemiological studies have been able to identify results observed for broad categories (herbicides, insecticides, fungicides), chemical classes (chlorophenoxy herbicides, carbamates, organophosphates, etc.) or several specific active substances (see tables on pages 143 to 146 of Annex 2 of the report "*Synthèse et Recommandations*" ["Summary and Recommendations"]); these tables list a large number of active substances that have been prohibited in France and Europe for many years, for which the strength of the presumed association with the occurrence of health effects was rated moderate or high, associated with a consistent mechanistic hypothesis. They essentially concern organochlorine insecticides, carbamates and organophosphates.

As the formal request to ANSES is to provide recommendations on MAs, only active substances for which the INSERM report notes a presumed association¹⁷ with one or more health outcomes and which are authorised in the European Union were examined. These active substances are as follows:

- chlorpyrifos;
- mancozeb and maneb;
- 2,4-D, MCPA and mecoprop;
- glyphosate.

¹⁶ <http://www.efsa.europa.eu/en/supporting/pub/497e.htm>

¹⁷ According to the rating defined by the group of experts.

The INSERM expert appraisal report however warns the reader: "For all the tables, the active substances mentioned are those that have been studied but are perhaps not the only ones involved".

These seven active substances each underwent a detailed comparative analysis using the three data sources.

4. ANALYSIS BY ACTIVE SUBSTANCE - CONSEQUENCES FOR MAS

4.1 Chlorpyrifos

- ✓ The INSERM expert appraisal report concluded that there is:
 - a moderate (+) presumed association between exposure to chlorpyrifos and occurrence of leukaemia in applicators, according to the results of a cohort study (Lee *et al.*, 2004¹⁸), supported by a consistent mechanistic hypothesis (++);
 - a weak (±) presumed association between exposure to chlorpyrifos and occurrence of NHL¹⁹ in farmers, according to the results of a case-control study (Waddell *et al.*, 2001²⁰), supported by a consistent mechanistic hypothesis (++)

The INSERM expert appraisal report notes genotoxic, pro-oxidant and immunotoxic properties of chlorpyrifos and a presumed association between exposure of applicators and the occurrence of some haematological neoplasms.

The EFSA literature review identified 26 studies investigating associations between generic pesticide exposure and the various forms of leukaemia. Significant results were found for seven different studies; with the exception of the AHS (Agricultural Health Study) cohort, all these studies were considered of mediocre quality. The meta-analysis showed a non-significant pooled effect (OR 1.26; 95 % CI 0.93-1.17)²¹ and had modest heterogeneity. The meta-analyses previously published by Merhi (2007)²² and van Maele-Fabry (2008)²³ suggested a statistically significant association, although weak, between occupational exposure to pesticides and all haematopoietic cancers. However, the authors emphasised the limitations of these studies, including the lack of data on exposure and the precise definition of exposure, the consideration of other risk factors and the precise definition of leukaemia type.

Regarding non-Hodgkin lymphoma, a wide variety of definitions were used in 44 epidemiological studies, of which 21 came from the AHS cohort (unspecified lymphomas, lymphoproliferative disorders, diffuse large cell lymphoma, follicular lymphoma, etc.). Five of these were prospective studies and seven investigated the association with biomarkers of exposure (organochlorines). Among these studies, no substance belonging, like chlorpyrifos, to the class of organophosphates was apparent in association.

It should be noted that the information available from the European assessment did not lead to any classification for mutagenicity or carcinogenicity being proposed. Moreover, a paragraph from the US EPA's preliminary document for the re-assessment of chlorpyrifos²⁴ (2011) mentions with

¹⁸ LEE WJ, BLAIR A, HOPPIN JA, LUBIN JH, RUSIECKI JA, et al. Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. *J Natl Cancer Inst* 2004a, **96**: 1781-1789.

¹⁹ NHL: Non-Hodgkin lymphoma.

²⁰ WADDELL BL, ZAHM SH, BARIS D, WEISENBURGER DD, HOLMES F, et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Causes Control* 2001, **12**: 509-517.

²¹ OR: odds ratio; CI: confidence interval.

²² MERHI M, RAYNAL H, CAHUZAC E, VINSON F, CRAVEDI JP, et al. Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. *Cancer Causes Control* 2007, **18**: 1209-1226.

²³ VAN MAELE-FABRY G, DUHAYON S, MERTENS C, LISON D. Risk of leukaemia among pesticide manufacturing workers: a review and meta-analysis of cohort studies. *Environ Res* 2008, **106**: 121-137.

²⁴ US EPA Memorandum. Chlorpyrifos: preliminary human health risk assessment for registration review, 30/06/2011.

regard to the AHS study that “the findings for lung cancer and colorectal cancer warrant further follow-up and additional research. Associations with breast and prostate cancer are weak, but also warrant monitoring the literature for additional publications on this association. There is no compelling evidence of an association with other cancer sites including pancreatic cancer, melanoma, brain, esophageal, kidney, all lymphohematopoietic cancers combined and NHL, leukemia, and multiple myeloma”.

- ✓ The INSERM expert appraisal report also concluded that there is a moderate (+) presumed association between *in utero* exposure to chlorpyrifos and neurodevelopmental disorders based on the results of a cohort study (Rauh *et al.*, 2006²⁵), supported by a consistent mechanistic hypothesis (++).

The INSERM expert appraisal report considers that indications of potential neurotoxicity of *in utero* exposure to pesticides, particularly organophosphates, have accumulated; for instance, associations with prenatal exposure to chlorpyrifos were observed at the age of 3 and 7 years in one study and show a decrease in overall IQ and working memory, with the existence of a genetic susceptibility (PON1²⁶) in the mother or child seeming to modulate the strength of these associations. Despite the reservations made about the fact that most studies were conducted in the United States in ethnic minorities or low-income populations subject to other environmental exposures and other vulnerabilities that may interfere with the observed associations, the INSERM experts concluded that there was a moderate presumed association.

The EFSA literature review addressed the issue of the impact of pesticides on neurodevelopment and mentions the existence of 31 epidemiological studies that have evaluated the association between pesticide exposure and certain aspects of neurodevelopment. The number of subjects in these studies varied from 25 to 1041. In 27 of these studies, exposure was estimated using a biological marker. A large number of pesticides were studied, most often organophosphates, either individually (chlorpyrifos, malathion) or as a group. The difficulties in synthesising these data were stressed, because of the heterogeneity and complexity of the methods used to assess the effects on neurodevelopment (35 exploratory methods including scales, scores, questionnaires, tests, etc.) that prevent the epidemiologic studies from being compared with each other.

The report states that no meta-analysis has been published regarding these effects. In addition, the epidemiological results concerned discrete effects and were not statistically significant for the vast majority. The conclusion of this literature review stressed that due to the large number and diversity of studies, these results should be interpreted with caution and that the level of evidence is insufficient to suggest an association between pesticide exposure and the occurrence of neurodevelopmental disorders.

Based on new data submitted on the toxicity of chlorpyrifos-ethyl (study of cholinesterase activity in young and adult rats after acute or repeated exposure²⁷), on 22 April 2014, EFSA published its conclusions on the re-assessment of the risk²⁸ of chlorpyrifos²⁹ that may lead to the adoption of new reference values, far more conservative than those previously determined (divided by 10), which will result in a risk re-assessment for all chlorpyrifos-ethyl products currently on the market.

The new toxicity reference values published by EFSA are as follows:

- ADI: 0.001 mg/kg bw³⁰/d;

²⁵ RAUH VA, GARFINKEL R, PERERA FP, ANDREWS HF, HOEPNER L, et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics* 2006, **118**: e1845-e1859.

²⁶ PON1: gene encoding paraoxonase 1, an enzyme involved in the detoxification of organophosphate molecules.

²⁷ Comparison of Cholinesterase (ChE) inhibition in young adult and preweanling CD Rats after acute and repeated Chlorpyrifos or Chlorpyrifos-Oxon exposures. M. S. Marty, Ph.D., A. K. Andrus, M.S. June 2010. (MRID 48139301). DAS Report No. K-044793-332; DAS Ref. G110. Unpublished.

²⁸ EFSA (European Food Safety Authority), 2014. Conclusion on the peer review of the pesticide human health risk assessment of the active substance chlorpyrifos. *EFSA Journal* 2014;12(4):3640, 34 pp. doi:10.2903/d.efsa.2014.3640 www.efsa.europa.eu/efsajournal.

²⁹ The active substance "chlorpyrifos" exists in two forms, chlorpyrifos (ethyl derivative) and chlorpyrifos-methyl; both have been approved in the European Union. The EFSA conclusions only relate to the ethyl form and the final decision of the European Commission is pending. Data on the methyl form are being analysed at European level.

³⁰ bw: body weight.

- AOEL: 0.001 mg/kg bw/d;
- ARfD: 0.005 mg/kg bw

The Acceptable Daily Intake (ADI) of chlorpyrifos-ethyl, established when it received approval, is 0.01 mg/kg bw/d. It was determined by applying a safety factor of 100 to the NOAEL obtained in two-year oral toxicity studies in rats, mice and dogs.

However, the ADI for chlorpyrifos-ethyl published by EFSA on 22 April is 0.001 mg/kg bw/d. It was determined by applying a safety factor of 100 to the NOAEL obtained in a comparative study of erythrocyte cholinesterase inhibition after repeated oral administration in rats.

The acceptable operator exposure level (AOEL) for chlorpyrifos-ethyl, established when it received approval, is 0.01 mg/kg bw/d. It was determined by applying a safety factor of 100 to the NOAEL obtained in 90-day oral toxicity studies in mice, rats and dogs.

However, the AOEL for chlorpyrifos-ethyl published by EFSA on 22 April is 0.001 mg/kg bw/d. It was determined by applying a safety factor of 100 to the NOAEL obtained in a comparative study of erythrocyte cholinesterase inhibition after repeated oral administration in rats.

The acute reference dose (ARfD) for chlorpyrifos-ethyl, established when it received approval, is 0.1 mg/kg bw/d. It was determined by applying a safety factor of 100 to the NOAEL obtained in acute delayed neurotoxicity studies via the oral route in rats.

However, the ARfD for chlorpyrifos-ethyl published by EFSA on 22 April is 0.005 mg/kg bw/d. It was determined by applying a safety factor of 100 to the NOAEL obtained in a comparative study of erythrocyte cholinesterase inhibition after single oral administration in rats.

Regarding the risk to consumers, this re-assessment should be conducted within a European framework and under the aegis of EFSA to identify the uses that will remain acceptable based on the new toxicity reference values when the European Commission has made its decision.

It should be noted that chlorpyrifos-ethyl and -methyl were among the substances most frequently found in the (French) Total Diet Study 2³¹. Thus, chlorpyrifos-ethyl is found in fruits, vegetables and *merguez* sausages, and chlorpyrifos-methyl in cereals, fruits, vegetables and products made from wheat or rice.

Given EFSA's conclusions and the expected impact of the revision of the toxicity reference values for chlorpyrifos on the acceptability of risks (within the meaning of Regulation (EC) No 1107/2009) for human health, a re-assessment of plant protection products containing chlorpyrifos should be conducted at the earliest opportunity, upon confirmation of the adoption of the new reference values at EU level. MA holders should submit the information required for this purpose.

It should be noted that in its Opinions on products based on chlorpyrifos-ethyl, ANSES is currently conducting a dual risk assessment, using the current values and the new values published by EFSA. It recommends using the new values without delay.

Moreover, it should be noted that no product containing chlorpyrifos intended for amateur use is currently on the market in France.

4.2 Mancozeb

- ✓ The INSERM expert appraisal report concluded that there is:
 - a moderate (+) presumed association between exposure to mancozeb/maneb and occurrence of leukaemia, on the basis of a nested case-control study in a cohort (United

³¹ Total Diet Study 2 (TDS 2): study conducted by ANSES; www.anses.fr/Documents/PASER2006sa0361Ra1.pdf

Farm Workers of America cohort, Mills *et al.*, 2005³²), not supported by a mechanistic hypothesis;

- a moderate (+) presumed association between exposure to mancozeb/maneb and occurrence of melanoma, based on the results of a nested case-control study in the AHS cohort (Dennis *et al.*, 2010³³), not supported by a mechanistic hypothesis;

The INSERM expert appraisal established its conclusions by aggregating epidemiological and mechanistic data relating to maneb with those on mancozeb, and the data specific to mancozeb appear incomplete.

Regarding haematopoietic cancers, some epidemiological studies did not distinguish cholinesterase-inhibiting carbamate insecticides from dithiocarbamate fungicides, which led to substances with very different toxicological profiles being studied together.

For the presumed association between leukaemia and mancozeb, the expert appraisal drew on the results of a nested case-control study in a cohort, and the risk values for leukaemia were only significant for women, without a consistent mechanistic hypothesis.

The EFSA literature review identified 26 studies investigating associations between generic pesticide exposure and the various forms of leukaemia. Significant results were found for seven different studies; with the exception of the AHS cohort, all these studies were considered of mediocre quality. The meta-analysis showed a non-significant pooled effect (OR 1.26; 95 % CI 0.93-1.17) and had modest heterogeneity. The meta-analyses previously published by Merhi (2007) and van Maele-Fabry (2008) suggested a statistically significant association, although weak, between occupational exposure to pesticides and all haematological cancers. However, the authors emphasised the limitations of these studies, including the lack of data on exposure and the precise definition of exposure, the consideration of other risk factors and the precise definition of leukaemia type. No specific link with exposure to mancozeb is mentioned.

For melanoma, the INSERM expert appraisal drew on a nested case-control study in the AHS cohort that shows a significant dose-effect relationship when using mancozeb/maneb (without distinction) for more than 63 days, and an excess risk when there is co-exposure to arsenic derivatives. In addition, the EFSA literature review states on completing the analysis of this study that these results were not reproduced in other studies. There is no consistent mechanistic hypothesis.

Lastly, it is important to mention the possibility of a link between Parkinson's disease and skin melanoma: treatments for the disease or the disease itself may quadruple the risk of developing melanoma (Ferreira *et al.*, 2010³⁴; Liu *et al.*, 2011³⁵).

- ✓ The INSERM expert appraisal report concluded that there is a weak (\pm) presumed association between exposure to mancozeb/maneb when **associated with exposure to paraquat**, and the occurrence of Parkinson's disease based on the results of a case-control study (Costello *et al.*, 2009³⁶), supported by at least one toxicity mechanism.

Numerous studies have shown a generic link between pesticide exposure and Parkinson's disease. Few studies have focused on fungicides. Studies in the general population in California have shown an association with maneb; mancozeb is not explicitly mentioned. The INSERM group of

³² MILLS PK, YANG R, RIORDAN D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. *Cancer Causes Control*. 2005, 16(7): 823-830.

³³ DENNIS LK, LYNCH CF, SANDLER DP, ALAVANJA MC. Pesticide use and skin melanoma in pesticide applicators in the agricultural health study. *Environ Health Perspect* 2010, 118: 812-817.

³⁴ LIU R, GAO X, LU Y, CHEN H. Meta-analysis of the relationship between Parkinson disease and melanoma. *Neurology* 2011, 76: 2002-2009.

³⁵ FERREIRA JJ, NEUTEL D, MESTRE T, COELHO M, ROSA MM et al. Skin cancer and Parkinson's disease. *Mov Disord* 2010, 25: 139-148.

³⁶ COSTELLO S, COCKBURN M, BRONSTEIN J, ZHANG X, RITZ B. Parkinson's Disease and Residential Exposure to Maneb and Paraquat From Agricultural Applications in the Central Valley of California. *Am J Epidemiol* 2009, 169: 919-926.

experts drew primarily on experimental and mechanistic data obtained with maneb, and on a presumed association qualified as weak with co-exposure to maneb and paraquat.

Although mancozeb and maneb are two chemically similar fungicides from the group of ethylene-bis-dithiocarbamates, they are regarded as distinct active substances for regulatory purposes and it is difficult to interpret the aggregate results of the epidemiological studies. The two active substances should be dealt with separately.

The European assessment of mancozeb found no carcinogenicity or genotoxicity. It should be noted that the study of developmental neurotoxicity conducted with mancozeb showed no effects in young rats at doses toxic to the mother and at dose levels that were teratogenic in the same species. The malformations noted in the teratogenicity studies of the draft European assessment report are most likely due to the thyroid-function inhibiting properties of ETU³⁷, one of the degradation products of mancozeb. The relative shares of direct effects of ETU on embryo-foetal development and toxic effects in the mother remain to be clarified.

These points should be updated in 2015³⁸ when submitting the application for renewal of approval of the active substance mancozeb, especially regarding the effects on the central nervous system and carcinogenic potential, as well as potential endocrine-disrupting effects (antithyroid effects of ETU). The application³⁹ should include a recent literature review and possibly additional studies.

ANSES recommends taking all of these points into account when the application for renewal of approval, scheduled for 2015, is submitted.

Regarding non-professional users specifically, it is necessary at the earliest opportunity to ensure that all products containing mancozeb and authorised for amateur gardening comply with the Decree and ministerial Orders of 30 December 2010 concerning the use of plant protection products by non-professional users.

4.3 Maneb

- ✓ The INSERM expert appraisal report concluded that there is:
 - a moderate (+) presumed association between exposure to mancozeb/maneb and occurrence of leukaemia on the basis of a nested case-control study in a cohort (United Farm Workers of America cohort, Mills *et al.*, 2005), not supported by a mechanistic hypothesis;
 - a moderate (+) presumed association between exposure to mancozeb/maneb and occurrence of melanoma, based on the results of a nested case-control study in the AHS cohort (Dennis *et al.*, 2008), not supported by a mechanistic hypothesis;

The INSERM expert appraisal established its conclusions by aggregating epidemiological and mechanistic data relating to mancozeb with those on maneb, and the data specific to maneb appear incomplete.

Regarding haematopoietic cancers, some epidemiological studies did not distinguish cholinesterase-inhibiting carbamate insecticides from dithiocarbamate fungicides, which led to substances with very different toxicological profiles being studied together.

For the presumed association with leukaemia, maneb is not specifically mentioned; the expert appraisal drew on the results of a nested case-control study in a cohort obtained with mancozeb (significant risk values for women).

The EFSA literature review identified 26 studies investigating associations between generic pesticide exposure and the various forms of leukaemia. Significant results were found for seven

³⁷ ETU: ethylene thiourea.

³⁸ The expiry date for approval of the active substance mancozeb was postponed to 31 January 2018 by Implementing Regulation (EU) No 762/2013 of 7 August 2013 amending Implementing Regulation (EU) No 540/2011.

³⁹ Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.

different studies; with the exception of the AHS cohort, all these studies were considered of mediocre quality. The meta-analysis showed a non-significant pooled effect (OR 1.26; 95 % CI 0.93-1.17) and modest heterogeneity. The meta-analyses previously published by Merhi (2007) and van Maele-Fabry (2008) suggested a statistically significant association, although weak, between occupational exposure to pesticides and all haematological cancers. However, the authors emphasised the limitations of these studies, including the lack of data on exposure and the precise definition of exposure, the consideration of other risk factors and the precise definition of leukaemia type. A specific link with maneb is not mentioned.

For melanoma, the INSERM expert appraisal drew on a nested case-control study in the AHS cohort that shows a significant dose-effect relationship when using mancozeb/maneb (without distinction) for more than 63 days, and an excess risk when there is co-exposure to arsenic derivatives. In addition, the EFSA literature review states on completing the analysis of this study that these results were not reproduced in other studies. There is no consistent mechanistic hypothesis.

Lastly, it is important to mention the possibility of a link between Parkinson's disease and skin melanoma: treatments for the disease or the disease itself may quadruple the risk of developing melanoma (Ferreira *et al.*, 2010⁴⁰; Liu *et al.*, 2011⁴¹)

- ✓ The INSERM expert appraisal report concluded that there is a weak (\pm) presumed association between exposure to mancozeb/maneb, when **associated with exposure to paraquat**, and the occurrence of Parkinson's disease, based on the results of a case-control study (Costello *et al.*, 2009), supported by at least one toxicity mechanism.

Numerous epidemiological studies have shown a generic link between pesticide exposure and Parkinson's disease. Few studies have focused on fungicides. The expert appraisal drew primarily on experimental data obtained with maneb from *in vitro* studies, focusing mainly on the disruption of neurotransmitters in cellular systems; however, extrapolation of the results of these studies to animals or humans has proved difficult. In epidemiological terms, a 1.75 times higher risk of Parkinson's disease was observed with co-exposure to maneb and paraquat, while there was no association in the event of exposure to just one of these two substances. This result may be supported by a consistent mechanistic hypothesis; indeed, several studies on animal models co-exposed to maneb and paraquat have shown some potentiation of the neurotoxic effects of the two active substances. These effects may be due to the disruption of neurotransmitter transport and an increase in oxidative stress.

Although mancozeb and maneb are two chemically similar fungicides from the group of ethylene-bis-dithiocarbamates, they are regarded as distinct active substances for regulatory purposes and it is difficult to interpret the aggregate results of the epidemiological studies. The two active substances should be dealt with separately.

The European assessment of maneb found no carcinogenicity or genotoxicity; this assessment will be updated regarding effects on the central nervous system, development and the carcinogenic potential, as well as potential endocrine-disrupting effects (antithyroid effects of ETU, a degradation product of maneb) in 2015⁴² when submitting the application for renewal of approval of the active substance maneb. This application should include a literature review and possibly additional studies.

ANSES recommends taking all of these points into account when the application for renewal of approval, scheduled for 2015, is submitted.

⁴⁰ FERREIRA JJ, NEUTEL D, MESTRE T, COELHO M, ROSA MM *et al.* Skin cancer and Parkinson's disease. *Mov Disord* 2010, **25**: 139-148.

⁴¹ Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. *Neurology* 2011, **76**: 2002-2009.

⁴² The expiry date for approval of the active substance maneb was postponed to 31 January 2018 by Implementing Regulation (EU) No 762/2013 of 7 August 2013 amending Implementing Regulation (EU) No 540/2011.

Moreover, it should be noted that no product containing maneb intended for amateur use is currently on the market in France.

4.4 2,4-D

- ✓ The INSERM expert appraisal report concluded that there is a moderate (+) presumed association between exposure to 2,4-D and the occurrence of NHL among **farmers**, on the basis of a nested case-control study in a cohort (Mills *et al.*, 2005, United Farm Workers of America cohort⁴³).

In cohort studies conducted in factories where 2,4-D, mecoprop and MCPA are manufactured, it has proved impossible to distinguish the substances individually and these have been designated by the generic term "phenoxy herbicides" or "chlorophenoxy herbicides".

The mechanistic data reported in the INSERM expert appraisal concern *in vitro* studies on cell systems, focusing mainly on the disruption of neurotransmitters; however, extrapolation of the results of these studies to animals or humans has proved difficult. The INSERM experts conclude that "it is impossible to provide arguments for or against a causal link between exposure to phenoxy herbicides and the onset of haematopoietic disorders", mainly because of the lack of a mechanistic hypothesis.

A search for occurrences of "2,4-D" in the EFSA literature review revealed a nested case-control study in the "United Farm Workers of America" (UFW) cohort that showed an association between the fact of working in areas where 2,4-D is used intensively and stomach cancer. However, the report stresses that this study has many limitations: low numbers of cases and controls, misclassification of exposure.

Regarding non-Hodgkin lymphoma, a wide variety of definitions were used in 44 epidemiological studies, of which 21 came from the AHS cohort (unspecified lymphomas, lymphoproliferative disorders, diffuse large cell lymphoma, follicular lymphoma, etc.). Five of these were prospective studies and seven investigated the association with biomarkers of exposure (organochlorines). Among these studies, no phenoxy herbicide was apparent in association.

It should be noted that the PMRA⁴⁴ (Canada) concluded in 2007 that 2,4-D could not be classified as a human carcinogen, due to the divergence of the results of epidemiological studies, the existence of confounding factors and the fact that mechanistic studies in animals proved negative. The US EPA, regarding the RED⁴⁵ for 2,4-D in 2012, based on epidemiological data and genotoxicity studies, came to an identical conclusion and 2,4-D was classified as "D - Unclassifiable as to human carcinogenicity".

New studies from the draft assessment report for re-approval (DRAR)⁴⁶ confirm that the target of 2,4-D is the kidney. As effects (not statistically significant) on thyroid function were observed at the highest dose in an extended one-generation reproductive toxicity study in rats, a discussion on the potential endocrine-disrupting effect of 2,4-D should be considered after establishment of characterisation criteria for endocrine disruptors at European level, which is being proposed by the rapporteur Member State.

The rapporteur Member State found no carcinogenicity or genotoxicity (request for an *in vivo* confirmatory test).

⁴³ MILLS PK, YANG R, RIORDAN D. Lymphohematopoietic cancers in the United Farm Workers of America (UFW), 1988-2001. *Cancer Causes Control*. 2005, 16(7): 823-830.

⁴⁴ PMRA: Health Canada Pest Management Regulatory Agency.

⁴⁵ RED: Re-registration Eligibility Document (document associated with the re-registration decision for the active substance).

⁴⁶ <http://dar.Efsa.europa.eu/dar-web/provision>

The toxicological classification is unchanged except for the sensitising potential; based on a new study (LLNA⁴⁷), this active substance is no longer considered as sensitising. It should however be noted that the "developmental neurotoxicity" and "developmental immunotoxicity" branch of the extended one-generation study (Marty, 2010⁴⁸) is available in the dossier submitted in the US and Canada but was not assessed because these data are not routinely required for the European assessment. Although 2,4-D is not considered neurotoxic under the CLP Regulation⁴⁹, it would nevertheless be interesting to assess these new data to verify that there is no warning sign.

In view of all the information in the draft assessment report for re-approval, the assessment remains unchanged and the reference values are confirmed; pending criteria from the European Commission on endocrine disruptors, as well as EFSA's conclusions on the application for renewal of approval of 2,4-D, it does not seem justified to modify the marketing conditions for products based on 2,4-D. This recommendation concerns products intended for amateur and professional use.

4.5 MCPA

- ✓ The INSERM expert appraisal report concluded that there is a weak (\pm) presumed association between exposure to MCPA and occurrence of NHL, on the basis of two grouped case-control studies (NHL and hairy cell leukaemia; Hardell *et al.*, 2002⁵⁰).

In cohort studies conducted in factories where 2,4-D, mecoprop and MCPA are manufactured, it has proved impossible to distinguish the substances individually and these have been designated by the generic term "phenoxy herbicides" or "chlorophenoxy herbicides". Moreover, in many epidemiological studies, it has not been possible to distinguish exposure to MCPA from exposure to 2,4-D, which has meant that no conclusions specific to this substance can be drawn.

The mechanistic data reported in the INSERM expert appraisal concern *in vitro* studies on cell systems, focusing mainly on the disruption of neurotransmitters; however, extrapolation of the results of these studies to animals or humans has proved difficult. The INSERM experts conclude that "it is impossible to provide arguments for or against a causal link between exposure to phenoxy herbicides and the onset of haematopoietic disorders", mainly because of the lack of a mechanistic hypothesis.

A search for the term "MCPA" in the EFSA literature review revealed no occurrence. Regarding non-Hodgkin lymphoma, a wide variety of definitions were used in 44 epidemiological studies, of which 21 came from the AHS cohort (unspecified lymphomas, lymphoproliferative disorders, diffuse large cell lymphoma, follicular lymphoma, etc.). Five of these were prospective studies and seven investigated the association with biomarkers of exposure (organochlorines). Among these studies, no phenoxy herbicide was apparent in association.

The European assessment showed that the main targets of MCPA are the kidney and liver; changes in certain haematological parameters (CBC⁵¹, haemoglobin, erythrocyte damage, anaemia) are sometimes found at very high doses. MCPA has no genotoxic potential *in vitro* and *in vivo*, nor carcinogenic or reprotoxic potential.

⁴⁷ LLNA: Local lymph node assay (test for assessing skin sensitising potential).

⁴⁸ Marty MS *et al.* 2010. 2,4-D: An F1-Extended One Generation Dietary Toxicity Study in CRL:CD (SD) Rats. Dow Chemical Company 081104 GLP Unpublished.

⁴⁹ Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

⁵⁰ HARDELL L, ERIKSSON M, NORDSTROM M. 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* 2002, **43**: 1043-1049.

⁵¹ CBC: complete blood count.

The INSERM expert appraisal report mentions the occurrence of leukaemia and the presence of neoplastic infiltrates in the liver in an 18-month study in mice (Takagi, 1990⁵²). This study was not selected for the European assessment because it lacked a certain amount of basic data such as biochemical parameters, while histology concerned only the liver. In addition, the increased incidence of neoplastic infiltrates and leukaemia was only observed at the lowest dose (40 ppm) and was not found at the other doses.

ANSES recommends taking all of these points into account when the application for renewal of approval of the active substance⁵³, scheduled for 2015, is submitted, with regard to products intended for amateur and professional use.

4.6 Mecoprop

- ✓ The INSERM expert appraisal report concluded that there is a weak (\pm) presumed association between **occupational** exposure to mecoprop and occurrence of NHL, on the basis of nested case-control studies in a cohort (CCSPH Cross Canada Study of Pesticides and Health; McDuffie *et al.*, 2001⁵⁴, 2005⁵⁵; Hohenadel *et al.*, 2011⁵⁶; Pahwa *et al.*, 2012⁵⁷).

In several epidemiological studies and especially cohort studies conducted in factories where 2,4-D, mecoprop and MCPA are manufactured, it has proved impossible to distinguish the substances individually and these have been designated by the generic term "phenoxy herbicides" or "chlorophenoxy herbicides".

The mechanistic data reported in the INSERM expert appraisal concern *in vitro* studies on cell systems, focusing mainly on the disruption of neurotransmitters; however, extrapolation of the results of these studies to animals or humans has proved difficult. The INSERM experts conclude that "it is impossible to provide arguments for or against a causal link between exposure to phenoxy herbicides and the onset of haematopoietic disorders", mainly because of the lack of a mechanistic hypothesis.

A search for the term "mecoprop" or "MCP" in the EFSA literature review finds no occurrence.

Regarding non-Hodgkin lymphoma, a wide variety of definitions were used in 44 epidemiological studies, of which 21 came from the AHS cohort (unspecified lymphomas, lymphoproliferative disorders, diffuse large cell lymphoma, follicular lymphoma, etc.). Five of these were prospective studies and seven investigated the association with biomarkers of exposure (organochlorines). Among these studies, no phenoxy herbicide was apparent in association.

The European assessment showed that the main targets of mecoprop and mecoprop-P are the kidney and the liver; haematological changes affecting the erythroid cell line (decreased red blood cell count, haematocrit and haemoglobin concentration) are sometimes found at the highest dose in some studies, in some species. It concluded that there was an absence of carcinogenic potential from mecoprop.

⁵² TAKAGI S. Chronic toxicity of 2-methyl-4-chlorophenoxyacetic acid (MCPA) in mice. *Tohoku J Exp Med* 1990, **160**: 97-107.

⁵³ The expiry date for approval of the active substance MCPA was postponed to 31 October 2017 by Implementing Regulation (EU) No 762/2013 of 7 August 2013 amending Implementing Regulation (EU) No 540/2011.

⁵⁴ MCDUFFIE HH, PAHWA P, MCLAUGHLIN JR, SPINELLI JJ, FINCHAM S, et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 2001, **10**: 1155-1163.

⁵⁵ MCDUFFIE HH, PAHWA P, ROBSON D, DOSMAN JA, FINCHAM S, et al. Insect repellents, phenoxyherbicide exposure, and non-Hodgkin's lymphoma. *J Occup Environ Med* 2005, **47**: 806-816.

⁵⁶ HOHENADEL K, HARRIS SA, MCLAUGHLIN JR, SPINELLI JJ, PAHWA P, et al. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. *Int J Environ Res Public Health* 2011, **8**: 2320-2330.

⁵⁷ PAHWA M, HARRIS SA, HOHENADEL K, MCLAUGHLIN JR, SPINELLI JJ et al. Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces. *Int J Cancer* 2012, **131**: 2650-2659.

ANSES recommends taking all of these points into account when the application for renewal of approval of the active substance⁵⁸, scheduled for 2015, is submitted, with regard to products intended for amateur and professional use.

4.7 Glyphosate

- ✓ The INSERM expert appraisal report concluded that there is:
 - a moderate (+) presumed association between exposure to glyphosate and occurrence of NHL in **farmers**, on the basis of several case-control studies, some pooled (all types of lymphomas: Eriksson *et al.*, 2008⁵⁹; Hardell *et al.*, 2002⁶⁰);
 - a weak (±) presumed association between **occupational** exposure to glyphosate and occurrence of foetal deaths according to the results of the Arbuckle retrospective cohort study (1998⁶¹, 2001⁶²).

Glyphosate is currently being reassessed at European level: the draft assessment report for re-approval (DRAR)⁶³ prepared by the rapporteur Member State (Germany) was made available for peer review to all Member States on 22 January 2014. The rapporteur Member State conducted a systematic re-assessment of all the studies on toxicity and absorption and distribution in the body, and on metabolism and elimination, taken into account in the previous assessment according to current quality standards (tests conducted according to OECD guidelines, whenever available); it also assessed more than 150 studies that had not been evaluated at European level for the first submission (glyphosate and some products). Only toxicity studies considered acceptable or at least supportive by current standards were selected for the risk assessment. Lastly, a comprehensive literature review was conducted: more than 900 scientific articles published between 2000 and 2013 as well as all available information on glyphosate and some of its products were analysed. All publications underwent an assessment in terms of their quality, relevance and robustness; they were used for the risk assessment only when these criteria were met.

In the DRAR, the toxicological profile of glyphosate was re-analysed: the lack of genotoxic, carcinogenic or reprotoxic potential was confirmed. It is proposed not to establish an ARfD; however it is proposed to amend the ADI and AOEL that were established in 2002 and to:

- establish the ADI and AOEL based on the NOAEL of 50 mg/kg bw/d established in the teratogenicity study conducted in rabbits, the most sensitive animal species:
 - by applying a safety factor of 100 for the ADI: 0.5 mg/kg bw/d (ADI currently in force 0.3 mg/kg bw/d); the ADI for glyphosate is also applicable to its metabolite AMPA;
 - by applying a safety factor of 100 and a 20 % correction to account for the low oral absorption of glyphosate, the proposed AOEL is 0.1 mg/kg bw/d (AOEL currently in force: 0.2 mg/kg bw/d)

⁵⁸ The expiry date for approval of the active substance mecoprop was postponed to 31 October 2017 by Implementing Regulation (EU) No 823/2012 of 14 September 2012 derogating from Implementing Regulation (EU) No 540/2011.

⁵⁹ ERIKSSON M, HARDELL L, CARLBERG M, AKERMAN M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int J Cancer* 2008, **123**: 1657-1663.

⁶⁰ HARDELL L, ERIKSSON M, NORDSTROM M. 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* 2002, **43**: 1043-1049.

⁶¹ ARBUCKLE TE, SEVER LE. Pesticide exposures and fetal death: a review of the epidemiologic literature. *Crit Rev Toxicol* 1998, **28**: 229-270.

⁶² ARBUCKLE TE, LIN Z, MERY LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspect* 2001, **109**: 851-857.

⁶³ <http://dar.Efsa.europa.eu/dar-web/consultation>

For NHL, it should be noted that in the DRAR, the rapporteur Member State assessed the two case-control studies (Hardell and Eriksson, 1999⁶⁴; Hardell *et al.*, 2002) and did not select them due to many limitations: multiple exposures that were poorly documented, small number of subjects reporting exposure to specific substances, recall bias, indirect sources of information on product use (interview with relatives for 43 % of subjects), uncontrolled confounding factors given the small number of exposed subjects.

Regarding foetal deaths, it should also be noted that the rapporteur Member State assessed the same studies as the INSERM experts and highlighted the limitations, especially since no mechanistic hypothesis can be advanced. Indeed, glyphosate has been investigated extensively in studies of reproductive toxicity or those examining potential endocrine-disrupting properties both *in vivo* and *in vitro*; these studies all proved negative. In contrast, studies of reproduction and development conducted on certain glyphosate products containing the surfactant POE tallow amine showed greater toxicity in pregnant females and fetuses (delayed ossification, skeletal malformations) than that of glyphosate alone.

The rapporteur Member State is not proposing to amend the European classification of glyphosate. Moreover, it believes that there are sufficient data to conclude that the toxicity of glyphosate-based products is greater than that of the active substance. The difference may be due to some co-formulants increasing the toxicity, including surface-active agents such as POE-tallow amines.

In order to conduct a comprehensive risk assessment of glyphosate-based products containing POE-tallow amines and to ensure adequate protection of operators, workers, bystanders, residents and consumers, reference values have been established for the substance with CAS No. 61791-26-2 that was considered particularly toxic:

- AOEL, ADI and ARfD 0.1 mg/kg bw (/day)
- AOEL by the respiratory route 0.0166 mg/kg bw/d

There are considerable differences of opinion between the INSERM report and the draft assessment report for re-approval (DRAR) (both assessments concern the same set of epidemiological and mechanistic references). The INSERM experts consider that there is a weak presumed association for the increased foetal deaths and a moderate presumed association for the NHL found in the epidemiological studies. However, the INSERM report concludes as to a lack of consistent mechanistic hypothesis.

It should be noted that the proposed new AOEL is derived from the assessment by the rapporteur Member State and has not yet been discussed at European level. It is therefore likely to evolve and the AOEL currently in force shall remain applicable.

Given the information available on the substance and its toxicology profile (only classified for very irritating effects to eyes), it is proposed to rely on the re-assessment of 322 glyphosate-based products⁶⁵ authorised in France that will be conducted after the re-approval of the active substance, for which the European assessment will be completed in late 2014. As suggested by the rapporteur Member State, particular attention will then be paid to the toxicity of some of the co-formulants used in these products. ANSES recommends ensuring that the co-formulant with CAS No. 61791-26-2 has been substituted by MA holders .

In the event of a refusal to renew approval, products containing glyphosate would be withdrawn from the market.

⁶⁴ HARDELL L, ERIKSSON M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer* 1999, **85**: 1353-1360.

⁶⁵ Dated 07/05/2014.

5. AGENCY CONCLUSION AND RECOMMENDATIONS

The results of the two literature reviews, one conducted by the INSERM group of experts, and the other by the EFSA expert panel, based on the same body of published data, show some differences in interpretation. This can be explained by the fact that the EFSA analysis was based on publications that were able to meet criteria relating to the method or degree of precision in the description/measurement of exposure. The inventory and publication selection methods were not explained in the INSERM expert appraisal report. Moreover, a comparison of the references cited in the INSERM report with those analysed by institutions responsible for risk assessment (EU, Health Canada, US EPA) reveals some divergences for several active substances. It is therefore difficult to reach a definitive conclusion. The critical analysis of all the scientific literature requested as part of the assessment and re-assessment of the active substances will probably help to clarify the reasons for these differences of interpretation.

It should nevertheless be noted that the vast majority of substances identified by the INSERM report as having a presumed moderate or strong association with the occurrence of health effects concern substances that are now prohibited.

In addition, a formal request was recently made to the EFSA Panel on Plant Protection Products and their residues (PPR Panel), following publication of the results of the EFSA literature review, for the preparation of a scientific Opinion investigating, from experimental toxicology data, the potential link between “pesticides” and Parkinson’s disease, as well as childhood leukaemia.

Five of the seven active substances identified by the INSERM expert appraisal report (2,4-D, MCPA, mecoprop and mancozeb/maneb) had a presumed association identified as weak in the expert appraisal. For these five, the previous assessments are not considered to be called into question by new data. European assessment relating to the re-approval process for these active substances is either underway (2,4-D) or planned, with the submission of dossiers in 2014 (mecoprop) or 2015 (mancozeb, maneb, MCPA). ANSES recommends taking into account all available information when the application for renewal of approval is submitted, especially information relating to the endocrine-disrupting potential once the criteria have been defined by the European Commission.

However, for products containing **mancozeb** for use by non-professional users, it is necessary at the earliest opportunity to ensure their compliance with the Decree and ministerial Orders of 30 December 2010 prohibiting the use of certain plant protection products by non-professional users and concerning the packaging requirements for plant protection products.

Regarding **chlorpyrifos**, given the publication of the conclusions by EFSA and the expected impact of the revision of the toxicity reference values on the acceptability of risks (within the meaning of Regulation (EC) No 1107/2009) for human health, a re-assessment of products containing this substance should be conducted at the earliest opportunity, upon confirmation of the adoption of the new reference values at EU level. MA holders will have to submit the information required for this purpose.

Regarding the risk to consumers, this re-assessment should be conducted within a European framework and under the aegis of EFSA to identify the uses that will remain acceptable based on the new toxicity reference values.

These recommendations relate only to chlorpyrifos-ethyl; data are currently being analysed at European level for the methyl form. Following this assessment, and in the event that the reference values are lowered for chlorpyrifos-methyl, the same approach as that recommended for chlorpyrifos-ethyl should be adopted.

Finally it should be noted that there is currently no product containing chlorpyrifos intended for amateur use on the market in France.

Regarding **glyphosate**, given the information available on the substance and its toxicological profile (only classified for very irritating effects on eyes), it is proposed to rely on the re-assessment of all glyphosate-based products that will be conducted after the re-approval of the active substance, for which the European assessment will be completed in late 2014. Particular attention will then be paid to the toxicity of some of the co-formulants likely to be found in these products.

Note that it is expected that the products will be re-assessed (re-registered) one year after renewal of substance approval, or withdrawn from the market in the event of non-approval.

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KEY WORDS

INSERM collective expert appraisal; epidemiology; pesticides; chlorpyrifos; mancozeb; maneb; 2,4-D; MCPA; mecoprop; glyphosate