Background Document for FIFRA Scientific Advisory Panel

"The *N*-methyl Carbamate Cumulative Risk Assessment: Pilot Analysis"

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I. Purpose

This document is meant to provide the members of the FIFRA Scientific Advisory Panel (SAP) and the public information regarding:

- ❑ Background and the general framework for the development of the cumulative risk assessment for the *N*-methyl carbamate group of pesticides;

- ❑ Summary of the procedures used to identify the *N*-methyl carbamate cumulative assessment group;

- ❑ A "roadmap" for the documents and presentations included in the four day SAP meeting scheduled for February 15-18, 2005.

The February 2005 meeting of the FIFRA SAP is the second in a series of scientific meetings concerning the cumulative risk assessment for the *N*-methyl carbamate pesticides. These scientific evaluations are important milestones as the Agency works toward the August 2006 deadline imposed by the Food Quality Protection Act (1996) for the reassessment of all pesticide tolerances on food. The first meeting held on December 4, 2004 involved the review of a white paper entitled "Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk" developed by the LifeLife Group Inc (LLG). The February 2005 meeting will highlight four important topics

- ❑ **Session 1:** Hazard assessment: laboratory method for measuring acetylcholinesterase (AChE) inhibition and empirical modeling of AChE inhibition and recovery data

- ❑ **Session 2:** Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) modeling for carbaryl

- ❑ **Session 3**: Groundwater exposure models

- ❑ **Session 4**: Exposure assessment: Pilot case study of the *N*-methyl carbamate exposure assessment.

II. Brief History: Cumulative Risk Under the FQPA

In assessing the potential health risks associated with exposure to pesticides, EPA's attention has historically focused on single pathways of exposure (e.g., pesticide residues in food, water, or residential/ non-occupational uses) for individual chemicals, and not on the potential for individuals to be exposed to multiple pesticides by all pathways (and routes) concurrently. In 1993, a report by the National Research Council (NRC) made several recommendations on how to improve the assessment of health risks posed by pesticides in the diets of infants and children (NRC, 1993). One recommendation included consideration of all sources of dietary and non-dietary exposures to pesticides and assessment of risks from exposure to multiple pesticides

that cause a common toxic effect. The NRC publication provided an example for five organophosphorus pesticides.

Several years after the publication of the NRC report, Congress passed FQPA in 1996 which instructed EPA to base its assessment of the risk posed by the pesticide chemical on aggregate (i.e., total food, drinking water, residential, and other non-occupational) exposure to the pesticide; FQPA also required EPA to consider available information concerning the combined toxic effects to human health that may result from dietary, residential, or other non-occupational exposure to chemicals that have a common mechanism of toxicity (i.e., cumulative risk). The Office of Pesticide Programs (OPP) has developed a guidance document for developing cumulative risks assessments under FQPA (USEPA, 2002a). This guidance document states that cumulative risk assessments differ from the single-chemical aggregate risk assessments both in focus and intent and that the objectives of a CRA are to:

- Define the characteristics of the exposure to a group of chemicals that act by a common mechanism of toxicity

- Estimate multichemical, multipathway risks reflecting real-world exposure to pesticides, including the changing patterns of residue levels as they relate to differences in location, time, and co-occurrence

- Identify significant contributors to risk

- Characterize the confidence in the conclusions and the uncertainties encountered in the assessment

- Facilitate a greater understanding of the potential results of changes in pesticide uses and possible mitigation activities.

Based on the above guidance and principles, OPP released the revised cumulative risk assessment for the organophosphorus pesticides (OP) in June 2002 (USEPA 2002b). In this assessment, OPP developed and demonstrated in detail the methods and parameters that should be considered in estimating cumulative risk associated with common mechanism pesticides by multiple pathways of exposure. Various aspects of the hazard and dose-response assessment and the exposure analyses were presented to both the SAP and the public for comment numerous times over the course of several years. Both the SAP and the public provided helpful and insightful comments and ideas which were incorporated into the revised OP cumulative risk assessment. OPP is currently developing a cumulative risk assessment for the *N*-methyl carbamate class of pesticides; the *N*-methyl carbamate cumulative risk assessment is the subject of the current SAP meeting.

III. Cumulative Risk Assessment of the *N*-Methyl Carbamates

A. Overview of Activities to Date

1. Determining the Common Mechanism Group

The first step of producing a cumulative risk assessment is to identify a group of chemicals that produce a common toxic effect(s) by a common mechanism of toxicity. OPP has developed a general framework for identifying the chemicals that belong to that group (USEPA, 1999a). The cumulative guidance states that, in determining this common mechanism group (CMG), careful attention should be given to a variety of factors including the mechanism of toxicity, the time dimensions of the toxic effects and exposure, and the pesticide exposure patterns and treatment scenarios. Thus, assessing the potential for two or more carbamate pesticides to act by the same mechanism involves the consideration of three principles: 1) they cause the same critical effect(s); 2) they act on the same molecular target at the same target tissue; and 3) they act by the same biochemical mechanism of action perhaps because they share a common toxic intermediate (Mileson, 1998). OPP found that the three principles were met for the ChE-inhibiting carbamates and judged that acetylcholinesterase (AChE) inhibition was a scientifically accepted mechanism of action for the carbamates which provides a sufficient basis for determining a common mechanism of toxicity for grouping carbamate pesticides (USEPA, 1999b).

Thus, OPP concluded that the pesticides that comprise the subgroup of *N*-methyl carbamates, based on their structural characteristics and similarity and their shared ability to inhibit acetylcholinesterase by carbamylation of the serine hydroxyl group located in the active site of the enzyme, should be designated as a CMG (USEPA, 2001).

2. Determining the Cumulative Assessment Group

Once the chemical members of a CMG are identified, a necessary follow-on step in assessing the cumulative risk of a common mechanism group (here, the *N*-methyl carbamates) involves selecting a subset of these CMG chemicals as a Cumulative Assessment Group (CAG). As the risk assessor proceeds with the cumulative assessment, it is important to determine candidate chemicals and uses, routes, and pathways from the CMG that may cause cumulative effects. As described in the Cumulative Guidance (USEPA 2002a), this subset of CMG chemicals is selected because not all chemicals grouped by common mechanism of toxicity should necessarily be included in a quantitative cumulative risk assessment. For example, initial cumulative assessments should not attempt to quantify risk resulting from chemicals with low hazard potential

or from minor exposure scenarios, but should instead focus on those chemicals that are likely to be risk contributors. Specifically, the CAG–and consequently the cumulative risk assessment–should exclude those chemicals, those chemical uses, and those exposure scenarios/routes/pathways for which risk and exposure does not contribute in any meaningful or substantive ways to the total cumulative risk picture1. Although a chemical(s) may be removed from the quantification of risk, the rationale for such decisions should be transparently explained. Thus, all chemicals that were grouped by a common mechanism of toxicity should be accounted for (qualitatively or quantitatively) in the final assessment.

OPP began the process of determining the members of the CAG by identifying those carbamates which contained the *N*-methyl structural moiety2. OPP then further narrowed the list of the potential CAG-candidates by reviewing OPP databases to determine those CMG members that have active food or residential registrations. Those carbamates which have neither food nor residential (non-food) current registrations were eliminated from further consideration for inclusion in the CAG.

Next, OPP investigated the presence, pattern, and magnitudes of residues in the USDA's Pesticide Data Program (PDP) database through 2002. Those chemicals for which PDP did collect residue data but did not detect any residues were eliminated from consideration from the CAG if there were no residential uses. No chemicals were excluded from the CAG as a result of this analysis. Finally, those chemicals or specific uses that are currently undergoing phase-out or cancellation were removed from the CAG. As was done with the OP assessment, chemicals currently undergoing phase-out or cancellation are not included in the CAG since exposures are expected to be zero at some point in the near future.

1 As stated in the Cumulative Guidance , "This focus on likely risk contributors is important ... since a large number of chemicals may increase the complexity and uncertainty with no substantial change in total exposure. (USEPA, 2002b).

2 Some exceptions were made as described in additional detail in the Federal Register Notice. For example, formetanate hydrochloride was included in this group due to its mode of action rather than its structural similarity to the N-methyl carbamates.

Based on the above information, OPP's final corrected and updated proposed list of *N*-methyl carbamates which OPP expects to include in the cumulative risk assessment for the carbamate pesticides is as follows:

- ❑ Aldicarb/Aldoxycarb
- ❑ Carbaryl
- ❑ Carbofuran
- ❑ Formetanate HCl
- ❑ Methiocarb
- ❑ Methomyl
- ❑ Oxamyl
- ❑ Pirimicarb
- ❑ Propoxur
- ❑ Thiodicarb

These carbamates all display ChE-inhibiting activity, have current active registrations, and are expected to contribute to the carbamate cumulative risk assessment through quantitatively meaningful exposure scenarios.

B. Developing the Exposure Scenarios

Detailed exposure scenarios for all of the uses remaining for each pesticide in the CAG need to be developed. This includes determination of potential human exposures by all relevant pathways, durations, and routes that may allow simultaneous exposures, or any sequential exposures among the CAG members that could contribute to the same joint risk of the common toxic effect (i.e., either by overlapping internal doses or by overlapping toxic effects). The framework for estimating combined exposures is based on exposure to individuals, representing differing attributes of the population (e.g., human activity patterns, place of residence, age) that link pathways/route of exposure through scenario building. Cumulative risk values for a given common toxic effect are calculated separately for each exposure route and duration and then combined. To the extent data permit, the temporal and spatial linkages should be maintained for the many factors defining a possible individual exposure. A decision must be made on the relative importance of scenarios and the need for their inclusion in a quantitative assessment, as well as on the populations of interest and locations for evaluation in the assessment. The potential for co-occurrence of possible exposure scenarios is evaluated. Spatial, temporal, and demographic considerations are major factors in determining whether a concurrent exposure is likely to occur. In other words, all exposure events need to occur over a specific interval of time; events need to agree in time, place, and demographic characteristics; and an individual's dose needs to be matched with relevant toxicological values in terms of route and duration.

EPA has performed this analysis and has included the identified exposure scenarios in the case study (See Estimation of Cumulative Exposure From *N*-Methyl Carbamates: A Case Study). Specifically, the key exposure scenarios include food, drinking water (surface water), and residential exposure on the lawn and in/around the home. The case study provides route-specific exposure estimates from three probabilistic exposure models (Lifeline, CARES, and DEEM/Calendex) for one region of the US (Southeast).

C. Evaluating the Appropriate Methodologies for Developing the CRA

The following text describes three key areas where methods are under development and/or EPA is soliciting comment from the SAP: a) Hazard assessment; b) Groundwater models; and c) Exposure assessment: Pilot case study of the *N*-methyl carbamate exposure assessment. These three areas are the major focus of the February, 2005 SAP meeting regarding the *N*-methyl carbamate cumulative risk assessment. The following text provides an overview of the issues and provides general context for the accompanying technical documents.

1. Cumulative Hazard Assessment

The Cumulative Guidance (USEPA, 2002a) describes several methods which could be used for performing cumulative hazard assessment. Some of these include use of effect levels from toxicology studies [e.g., no-observed-adverse-effect (NOAELs) and/or lowest-observed-adverse-effect levels (LOAELs)]; benchmark dose modeling (USEPA, 2000b); and also physiologically-based pharmacokinetic/pharmacodynamic models (PBPK/PD). Each of these methods is considered reasonable approaches to performing cumulative hazard assessment. The *N*-methyl carbamate pesticides inhibit AChE through carbamylation of the active. Inhibition is followed by rapid recovery. This rapid recovery is a unique toxicological characteristic for this group and is thus an important characteristic for consideration in the cumulative risk assessment. These issues have provided opportunity for direct collaboration between OPP and scientists at EPA's National Health and Environmental Effects Research Laboratory (NERL) and National Exposure Research Laboratory (NERL). Issues related to the pharmacokinetics (PK) and pharmacodynamics (PD) of recovery will discussed throughout the February SAP meeting, particularly during Sessions 1, 2, and 4.

EPA used the relative potency factor (RPF) method in its cumulative risk assessment of the OPs. EPA will likely rely primarily on the RPF method in the *N*-methyl carbamate cumulative risk assessment. Briefly, with the RPF approach, the toxic potency of each chemical is first determined. The determination of toxic potency should, to the extent feasible with available data, be conducted on a uniform basis (i.e., same measure of potency, for the same effect, from the same test species/sex

using studies of comparable methodology). An index chemical is used as the point of reference for standardizing the common toxicity of the other chemical members of the CAG. Session 1 of the SAP meeting will highlight key areas important to determining relative potency for the *N*-methyl carbamates. Specifically, laboratory methods for measuring ChE inhibition and empirical modeling of dose-response and time course data will be discussed on Session 1.

Consistent with EPA's commitment to improve techniques and methodologies for developing cumulative risk assessments, EPA will present two different PK and/or PD approaches—simple PK empirical approach for exposures to multiple *N*-methyl carbamates (Session 1) and physiologically-based pharmacokinetic/ pharmacodynamic (PBPK/PD) model for carbaryl (Session 2). Although there are practical limitations which may prevent the use of these approaches in the quantitative cumulative risk estimation for the *N*-methyl carbamates at this time, they do provide qualitative hazard and risk characterization and also demonstrate EPA's on-going efforts to improve cumulative risk assessment methods.

a. Laboratory Methods for Measuring AChE Inhibition

Typical studies submitted to EPA by pesticide registrants are performed use some variation of the Ellman technique (Ellman et al, 1961) This method involves sample dilution, prolonged incubation, and physiological temperatures, all of which promote reversal of the enzyme inhibition. If precautions are not taken to prevent recovery using this method, then reported AChE activities can underestimate actual AChE inhibition and could thus impact relative potency estimates (Winteringham and Fowler, 1966). Furthermore, the reversibility encountered during the assay varies for each carbamate, such that a standard correction factor cannot be used. A radiometric method as that reported by Johnson and Russell (1975) provides a more appropriate method for measure AChE inhibition as factors which promote reversibility are minimized. Laboratory scientists from EPA's NHEERL have systematically evaluated AChE inhibition following acute rat exposures to seven *N*-methyl carbamates using both Ellman and radiometric techniques. The results of these studies have been compared to results of acute rat toxicity studies submitted to EPA for purposes of pesticide registration. EPA will discuss the results of these experiments on Session 1 of the February, 2005 meeting.

b. Empirical dose-response modeling: Benchmark dose estimates

OPP is working collaboratively with NHEERL to develop relative potency estimates for the *N*-methyl carbamates. Relative potency will be based on benchmark dose estimates using AChE data extracted from rat toxicity studies. The empirical model used to calculate the BMDs been described in the documents provided to the FIFRA SAP. The exponential model proposed is similar to that used in the cumulative risk assessment of the OPs and previously endorsed by the FIFRA SAP (2001a, 2002).

c. Simple, pharmacokinetic model

The RPF method considers the dose-response component of inhibition but does not quantitatively consider recovery of AChE inhibition. A more refined approach would consider such toxicological behavior. EPA will present to the panel a simple, empirically based pharmacokinetic approach for incorporating recovery into risk estimates. This approach is similar in concept, although quantitatively different in application, to that proposed by individual panel members at previous SAP reviews (L. Rhomberg, 2002; D. Hattis, 2004). This PK approach assumes that the reactivation of enzyme is the main determinant of the recovery phase of AChE inhibition. The mathematical derivation and a simple, illustrative example of the approach are provided.

d. Physiologically-Based Pharmacokinetic Model Based Approach

The FIFRA SAP has previously encouraged OPP to consider using PBPK/PD models (FIFRA SAP 2001a, 2002) in developing cumulative risk assessments. In December 2003, EPA discussed with the FIFRA SAP aspects of a draft strategy for including PBPK/PD modeling into its cumulative risk assessment. Key issues included in the December 2003 review included the key data needed to support parameterization of a PBPK/PD model and the basic structure for a multi-chemical model appropriate for the *N*-methyl carbamate pesticides.

PBPK/PD models are data and resource intensive. As discussed in the cumulative guidance, the level of refinement for each cumulative risk assessment will depend on several factors; specifically included among these is the availability of adequate and appropriate data for the particular common mechanism group of interest. Very few PBPK models have been used by EPA's IRIS program (Integrated Risk Information System), and OPP has not

used such models to support pesticide registration (or for developing cumulative risk assessments). Scientists from OPP and ORD's National Exposure Research Laboratory (NERL) are collaborating on the multi-chemical-PBPK/PD case study in order to gain experience for developing a PBPK/PD model that is sufficiently robust for regulatory purposes. Given the early stage of development of these models, it is not known to what extent the PBPK/PD model can be used for cumulative risk assessment of the *N*-methyl carbamates.

Pharmacokinetic (PK) and pharmacodynamic (PD) data provide the basis for the development and evaluation of any PBPK/PD model. OPP has systematically evaluated the availability of PK and PD data for the *N*-methyl carbamates and has determined that for the majority of *N*-methyl carbamates the databases are not sufficiently complete for developing compound specific PBPK/PD models. PK studies typically submitted to OPP for purposes of pesticide registration were designed to evaluate absorption, distribution in tissues and organs, metabolism and elimination in fluids and excreta. The study protocols, however, were not specifically designed to obtain parameter values needed for developing robust PBPK/PD models. For example, sample collection is typically not targeted or specified to obtain blood/tissue partition coefficients or kinetic rates of metabolism or AChE inhibition for particular chemicals that may be identified with the critical metabolic pathways, or mechanisms of action. In addition, the guidelines require absorption, distribution, metabolism, and elimination (ADME) studies be initially performed only for the oral (gavage) route of administration. Ideally, oral, dermal and intravenous pharmacokinetic studies are needed to quantitatively distinguish between the kinetics of distribution, metabolism, and excretion from the kinetics of each absorption route. Lastly, radiometric measurements of tissue concentrations are not sufficient to identify the specific metabolites that would constrain the parameter values associated with chemical ADME. Therefore, mass balance of parent chemical and metabolites in tissues must be inferred from excretion data as mass equivalents remaining.

Although relevant PK data are not available for most of the *N*-methyl carbamates at this time, key data are available for carbaryl. As discussed in Use of Pharmacokinetic data to Refine Carbaryl Risk Estimates from Oral and Dermal Exposure (USEPA, 2004), metabolism studies specifically designed for purposes of evaluating pharmacokinetics and for developing a PBPK/PD model have been recently performed for the single chemical (aggregate) assessment of carbaryl. OPP is aware of on-going two efforts to develop a PBPK/PD model for carbaryl: ORD's NERL and the CIIT Centers for Health Research. The current status of NERL's efforts

will be presented to the SAP during the February, 2005 meeting (Session 2). EPA will solicit comment regarding PBPK/PD model structure, completeness of the carbaryl data, and statistical analyses.

2. Cumulative Exposure Assessment

People can be exposed to *N*-methyl carbamate pesticides through food, drinking water, and in and around residences. EPA has developed a pilot exposure assessment for the *N*-methyl carbamate pesticides that includes each of these pathways (Session 4). The pilot analyses are based on actual data and exposure scenarios for each member of the CAG. Results from three different exposure models (Lifeline, CARES, and DEEM/Calendex) are included in the case study. These models have been previously evaluated by FIFRA SAP on multiple occasions, most recently during the April, 2004 SAP meeting devoted to model comparison.

a. Food Exposure

The methods to develop estimates of exposure through the food exposure pathway are similar to those used in the cumulative risk assessment for the OPs (USEPA, 2002b) The cumulative assessment considers the food contribution of each of the 10 *N*-methyl carbamates as they occur in PDP data, in PDP-translated data, and in FDA data. The food exposure assessment is considered to be highly refined because it is based on residue monitoring data from the USDA's Pesticide Data Program supplemented by information from the Food and Drug Administration's Surveillance Monitoring Programs and Total Diet Study, where available and appropriate. In addition, the food component of the assessment incorporates actual consumption data from USDA's Continuing Survey of Food Intake by Individuals (CSFII), 1994-96/1998. EPA has conducted an exploratory analysis of the timing of food exposures at the high end of the exposure distribution. This analysis is described in Section IV of the case study. EPA is soliciting comment from the FIFRA SAP regarding conceptual and specific aspects of this analysis.

b. Drinking Water Exposure (Surface and Ground water)

Exposure to *N*-methyl carbamates can occur from surface- and ground-water sources of drinking water. On Session 3 of the February, 2005 meeting, OPP will solicit comment from the SAP on the use of one or more existing ground-water models to provide a pilot ground-water exposure assessment for the carbamates. OPP will present an evaluation of ground-water models under consideration and a conceptual model describing what the water models represent and how they would be used in the cumulative assessment. The pilot exposure analysis provides estimates of drinking water exposure based on PRZM-EXAMS modeling of a SE portion of North Carolina. The methods used to estimate surface water exposure are consistent with those used in the cumulative risk assessment of the OPs (USEPA, 2002b)

c. Residential Exposure

The residential component of the pilot analysis reflects indoor crack and crevice, lawn care, home garden, and pet collar uses for the three NMCs that have these registered residential uses and are used in the SE region of the U.S. These exposure scenarios may result in potential exposure via the oral (via hand-to-mouth activity in children), dermal, and inhalation routes. The assessment incorporates and reflects seasonal variations in pesticide use patterns and opportunities for exposure specific to and consistent with that region, and is based on a probabilistic approach in which a number of data sources were used to define how pesticides are used, how quickly they dissipate, how people may come into contact with pesticides via the dermal and inhalation pathways, and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn).

3. Topics Not Addressed at February, 2005 SAP

Cumulative risk assessments are large and complex. Each of the major components of the cumulative risk assessment (hazard; food, drinking water, residential exposure) are included in the documents prepared for the February 2005 meeting of the FIFRA SAP. The documents, issue papers, and panel questions developed by EPA emphasize methodology development and as such, do not encompass all aspects of the *N*-methyl carbamate cumulative risk assessment. It is important to note that there are topics not discussed in these documents which the Agency acknowledges are critical for the cumulative risk assessment.

Some key topics not addressed include:

- ❑ Identification of uncertainty and extrapolation factors (intraspecies, interspecies, and the FQPA 10X factor for the sensitivity to infants and children)

- ❑ Selection of the index chemical

- ❑ Determination of the specific sex and/or biological compartment (brain or blood) which will provide the basis for the relative potency estimates

- ❑ Estimates of margins of exposure are not provided.

These topics are not the subject of questions to the panel for the current SAP review. EPA is developing its cumulative risk assessment for the *N*-methyl carbamates in a deliberate, stepwise, and transparent manner. The current scientific review is important step as the Agency works toward the release of the *N*-methyl carbamate cumulative risk assessment in the spring of 2005.

IV. Summary

In 1996, passage of the Food Quality Protection Act (FQPA) imposed OPP the requirement to consider potential human health risks from all pathways of dietary and non-dietary exposures to more than one pesticide acting through a common mechanism of toxicity. FQPA also requires that all pesticide food tolerances must be reassessed by August, 2006. EPA's goal is develop a scientifically sound cumulative risk assessment using available tools. The SAP meeting scheduled for February, 2005 is an important milestone as EPA works towards the release of the preliminary cumulative risk assessment for the *N*-methyl carbamates (expected in Summer 2005). This peer review will consist of four sessions; each session will focus on a separate topic. Separate technical documents have been prepared for each topic.

- ❑ **Session 1:**

Cumulative Hazard Assessment: Issues for the FIFRA SAP
Appendix 1. General Protocol for the Acute Time Course and Dose-Response Studies of the Individual Carbamate Pesticides in Adult Male Rats
Appendix 2. Time course and dose-response plots for seven *N*-methyl carbamates
Appendix 3. Computational details for the empirical dose-time-response and simple PK risk assessment models
Appendix 4. R Source code for the simple pharmacokinetic risk assessment model example
Executable file: CarbUtils_1.0
Executable file: RAexample1.R

- **Session 2:**
  Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) modeling for carbaryl: Assessment of Carbaryl Exposure Following Turf Application Using a Physiologically Based Pharmacokinetic Model
  Loading and Operating Instructions for ERDEM
  Executable file: ERDEM Feb 2005 SAP PDF2.tmp

- **Session 3:**
  Groundwater exposure models
  The N-methyl Carbamate Cumulative Risk Assessment: Drinking Water Exposure Assessment for Ground Water
  Evaluation of Vadose-Zone Solute-Transport Models for USGS Agricultural Chemical Transport Studies and EPA's Office of Pesticide Programs (USGS report)

- **Session 4:**
  Estimation of cumulative exposure from *N*-methyl carbamate pesticides: A Case Study of 10 *N*-methyl carbamates.

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