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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

December 9, 2008

MEMORANDUM

SUBJECT: EPA's Response to the Questions and Issues Submitted by Gowan Regarding MRID 47262502 (Memo: 10-14-2008 and e:mail of 11-6-2008)

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HED has provided below detailed responses to the questions posed by Gowan in their October, 2008 letter to the Agency and in their November 6, 2008 e-mail.

INTRODUCTION: The Agency appreciates efforts by Gowan to clarify a variety of issues identified by HED during the review of MRID 47262502. The remaining questions posed by Gowan in the October, 2008 letter and follow-up November 6, 2008 e-mail fall in two broad categories: 1) laboratory protocol issues related to the acetylcholinesterase (AChE) measurements at Charles River Laboratories (CRL); 2) re-analysis of samples while the study was being conducted. At the October 29, 2008 meeting between OPP and Gowan, much of the discussion focused on the issue of

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combining data from Day 1 and Day 2. Each of these issues is discussed in this memo. This memo responds to Gowan's questions of October, 2008. Attachment A provides responses to the November e-mail.

SUMMARY: Regarding laboratory protocol issues at CRL for organophosphate pesticides (OPs), studies are not being rejected by HED solely based on this issue. In fact, as of early November, 2008, no OP study conducted by CRL during the period of approximately 2000-2007 has been rejected solely based the protocol issues. Instead, except for MRID 47262502, all others reviewed so far have been determined to be 'acceptable'. Although, the AChE protocol used by CRL may have contributed to the variability observed in MRID 47262502, protocol issues at CRL are secondary to those discussed in detail below.

Regarding the re-analysis of samples during the conduct of the study, Table 1 provides a tally of the number of samples re-analyzed in MRID 47262502 for RBC (females) and brain AChE inhibition. This table shows that the majority of re-analyzed samples are from Day 2, particularly for the female RBC ChE samples where 20 samples from Day 2 animals were re-analyzed but only 4 from Day 1 rats. These data suggest that some unknown condition or factor occurred on Day 2 that was different from the laboratory conditions on Day 1 leading to more samples being re-analyzed.

Table 1 Number of samples re-analyzed in MRID 47262502.

Female RBC ChE				
Group	**Day 1**		**Day 2**	
(mg/kg/day)	**Process 1**	**Process 2**	**Process 1**	**Process 2**
0	-	-	5	1
30	-	-	1	1
40	-	-	2	1
50	1	-	1	3
60	3	-	-	-
90	-	-	1	2
120	-	-	1	1
Brain ChE				
Group	**Males**		**Females**	
(mg/kg/day)	**Day 1**	**Day 2**	**Day 1**	**Day 2**
0	0	0	0	0
30	0	1	0	0
40	0	1	1	0
50	0	1	2	0
60	0	3	0	0
90	0	1	0	0
120	0	3	0	0

Differences in Day 1 and 2 are further evidenced by differences observed in RBC and brain AChE data. For example, at 30 mg/kg/day, 0-8% RBC ChE inhibition was

observed in females from Day 1 whereas 14-23% was observed in Day 2 animals. At the 90 and 120 mg/kg/day groups, male rats from Day 1 showed 1-3% brain AChE inhibition whereas the Day 2 rats from these dose groups exhibited 19-30% brain AChE inhibition. Some variability is expected in studies, particularly those like MRID 47262502 where dosing and sacrifice are staggered on different days, but the noted differences are larger than are typically seen in other rat studies with similar sample sizes (USEPA, 2002).

Based on the discussions between HED, Gowan, and Robert Sielken at the October 29, 2008 meeting, it is HED's understanding that the decision to evaluate the results of Day 1 and Day 2 together or separately remains an area of disagreement between Gowan and HED. Gowan has used a statistical approach to combine the data from Day 1 and Day 2. HED believes that both biological and statistical considerations to reviewing the data are warranted. With this in mind, and in order to assure that we are being health protective, HED believes that it is appropriate to consider the Day 1 and Day 2 data separately in determining the NOAELs and LOAELs from the study. HED has considered the written comments and information provided at the meeting

Detailed Responses to Questions Posed by Gowan:

1. ChE methodology

HED has suggested that variability was a consequence of flawed ChE methodology but has been unresponsive to our repeated queries regarding what should have been done differently in our study.

"Due to protocol issues for comparative cholinesterase assays performed at the testing facility, further scrutiny of the cholinesterase data was conducted during this review." [DER Page 2]

- We have requested but have not received clarification regarding how protocol issues with other ai's are relevant to the phosmet study. Were the cited comparative cholinesterase assays (CCA) protocol issues for carbamates or OPs? Were the cited protocol issues associated with pup or adult ChE results? Which sex or compartment was problematic? Which specific assay parameters in the CCA studies were of concern to the Agency?

- We have received no response from HED to our detailed submission of May 5 regarding specific aspects of the Charles River Laboratories (CRL) assay methodology. What specific aspects of the methodology used in our study should have been done differently?

- We used best available ChE assay methods and instrumentation at a contract research laboratory. The method was consistent with all available Agency guidance and was cross-validated with ORD. No other method had been validated by CRL at the time of study conduct. Since a validated method is necessary, what alternative method should we have used?

HED Response:
Regarding the statement in the dermal DER "Due to issues for comparative cholinesterase assays performed at the testing facility, further scrutiny ... .", HED would like to clarify that the "further scrutiny" on the AChE data was specific to the samples not

replicating (Process 1 and 2 on each day) and the lack of reasonably consistent inhibition (Day 1 to Day 2), which is not typical of AChE data. HED has informed Gowan on multiple occasions (January 24, 30, and 31; March 28; and April 9, 2008) that the issue with the dermal study is mainly due to the inconsistencies noted in the AChE data, specifically Day 1 and Day 2, Process 1 and Process 2 data, and the apparent inconsistent handling of the data. These inconsistencies were identified during the initial review of the study, which was performed without knowledge of the protocol issues for AChE activity assays at the testing facility. However, after meeting and discussing these inconsistencies with Gowan our concerns regarding the inconsistent handling of the AChE data, HED's concerns were addressed, in part, by the re-evaluation of the AChE data in the new statistical analysis submitted on May 5, 2008. As noted above, HED is still concerned about the differences in inhibition observed on Day 1 and Day 2 as well as the lack of sample replication of Process 1 and Process 2 data.

The protocol issues with CRL are multifaceted. They impact OPs and N-methyl carbamates (NMCs) to different degrees and differ between adult and juvenile studies. In general, the Agency's concerns with the CRL protocol impact the NMCs to a greater degree than OPs due to washing of the samples, which results in reactivation of the AChE, and thus underestimation of AChE inhibition, with NMCs. HED has reviewed studies conducted by CRL during the period of 2000-2007 (the approximate period when the protocol in question was being used) for both OPs and NMCs, from studies in adults and juveniles, and from both oral and dermal exposures. As of early November, 2008, HED has not rejected any study with an ***OP*** conducted at CRL solely on issues related to the AChE protocol. Moreover, HED has done a review of the acute comparative AChE phosmet study conducted by CRL and found it to be "acceptable."

In the summer of 2007, EPA became aware of issues with the protocol being used by CRL to measure AChE inhibition. Since that time, EPA has had several conference calls with CRL. The meetings have varied in scope from issues on a specific study/chemical to more general issues surrounding the CRL protocol. For example, HED and ORD participated in a conference call with CRL, Gowan, Gowan study monitor Gail Arce, FMC, and Cheminova on January 31, 2008, to discuss general issues related to the CRL protocol. Although the phosmet dermal study was not directly discussed at this meeting due to CBI concerns, the general CRL protocol issues discussed would apply to this study. Overall, there are several general concerns held by HED regarding the CRL protocol from 2000 to 2007. These impact OPs and NMCs differently and include the dilution factors, time for homogenization of the brain, lysing of RBCs, and the length of time from sample collection until analysis used during this period. It is notable that CRL has since that time made changes to the AChE protocol to address these issues.

In regards to the May 5, 2008 submission, HED has responded by discussing the information contained in the May 5, 2008 submission at the meeting with Gowan on May 8th, and provided a written response on June 25, 2008 (TXR# 0054871). HED did not provide detailed responses concerning the CRL assay methodologies since these issues are not the critical consideration in the review. The remaining primary concern pertains to the lack of replicability of Process 1 and 2 and Day 1 and Day 2 data.

2. Variability

- **We have received no response to our March 23 statistical analysis showing that the variability in our study was comparable to or less than that seen in ORD studies. Should this not be considered when evaluating the variability seen in our study?**

- **We noted up to 3.6x differences in control animal responses as well as "reversed" control responses in the ORD data presented in Docket OPP-2007-1088-0038. Should this typical variability not be considered when evaluating our study?**

- **What standards for cholinesterase variability are we being held to? If there are standards, when were these published and have they been peer reviewed?**

HED Response: The Agency appreciates the statistical evaluation submitted by Gowan, and based on recent discussion, the assessment will be considered in an update to the DER. The key issue in the phosmet dermal study relates to replicability, particularly with regard to amount of inhibition observed between Day 1 and Day 2 and Process 1 and Process 2.

The questions above mention ORD studies with NMCs. ORD researchers have shown in a variety of experiments for NMCs that they are able to replicate brain and blood AChE inhibition across experiments when using the same chemical and dose. This was not found in the phosmet study (Process 1/Process 2). The variability in the controls referenced by Gowan is not relevant to the Day 1/Day 2 discussion because it is the amount of inhibition; *i.e.,* percent change from control, which was not replicated in the phosmet study.

As a further example of the typically low variability expected in AChE data from an OP study collected from different animals and on different days, HED has tabulated data from the phosmet subchronic neurotoxicity study (MRID 44811801). In this table, data are shown at two points in time (3 and 7 weeks of dosing). Typically for OPs, steady state inhibition of brain AChE is reached at or near 2-3 weeks of exposure. After this period of dosing, brain AChE responses tend to be very similar from 3 weeks of exposure up to 700 days or longer. Data shown here from the subchronic neurotoxicity study are consistent the typical OP pattern of brain AChE inhibition. For purposes of the current memo, it is important to note that the degree of inhibition varies to some degree but is similar between the time points. These data were derived from animals sacrificed on different days, not unlike the phosmet dermal study.

Table 2. % Cholinesterase Inhibition (brain)			
Time Interval	**Low dose**	**Mid dose**	**High dose**
phosmet subchronic neurotoxicity study – males			
Week 3	1.5%	10.8%	49.4%
Week 7	2.0%	17%	43.1%
phosmet subchronic neurotoxicity study – females			
Week 3	6.6%	10.8%	61.3%
Week 7	10%	19.5%	67.8%

3. Re-assays

"The latest submission from Gowan does not alter the conclusion of HED since none of the concerns raised in the DER have been addressed by Gowan. Specifically, a NOAEL

determination for the perturbation of RBC or brain cholinesterase activity by phosmet following repeat dermal exposure is not possible, based on the 21-day dermal exposure study (MRID 47262502). This conclusion is based on the lack of consistency/reproducibility of the cholinesterase activity measurements and the lack of a clear rationale for reanalyses, in addition to questionable practices with respect to data generation" [EPA June 25 memo, pages 1-2]

- The allegation of "questionable data practices" in a public document without any explanation is an extremely serious legal issue. What practices were considered questionable and why?
- The intent of re-assays was on-study quality control checks. These were real time and rapid judgment calls of study personnel. Less than 10% of the total samples were re-assayed. Suspected high as well as suspected low samples were selected for re-assay. Since an independent biostatistician (Sielken and Associates) did not use the re-assay data, why is this issue not moot?
- A miscommunication between the biostatistician and the study staff regarding the re-assays, including a set of 5 re-assayed control data points, was immediately reported and corrected. We have explained and apologized for the error. What was incomplete about our explanation?
- All data were reported. We used an independent biostatistician to analyze all data after these were collected. Since it was unknown at the time of data collection how the data would be analyzed, in what way was the study biased, as has been implied by HED?

HED Response: HED regrets the use of the phrase "questionable data practices" in our June 25 memo, and would like to clarify our concerns about sample handling in the laboratory, and subsequent statistical analysis of the data. With regard to the data generation practices, HED's concerns refer to the apparent *ad hoc* nature of decisions that were made in the lab to re-analyze samples.

Gowan states in the October, 2008 document that the intent of the re-assays was on-study quality control checks that were "real time and rapid judgment calls of study personnel". Gowan has stated to HED that this re-analysis was made without a pre-established set of

criteria. Without such criteria, the re-analysis was not done in a consistent fashion. As shown in Table 1 above, these 'quality control checks' were not done in a random way but occurred more often on Day 2. Moreover, the lack of criteria led to inconsistency in which samples were re-analyzed. For example, in the 50 mg/kg/day group, Day 1/Process 1 AChE values, rat #27651 displayed a value of 1.346 compared to the other values in that group (0.789-1.094). It is unclear to HED why this treatment sample was not re-analyzed when two control samples with similar values were re-analyzed. As such, all samples and re-analyses were not treated the same. Moreover, qualitatively different responses were observed on Day 1 and Day 2. For example, at 30 mg/kg/day, 0-8% RBC ChE inhibition was observed in females from Day 1 whereas 14-23% was observed in Day 2 animals. At the 90 and 120 mg/kg/day groups, male rats from Day 1 showed 1-3% brain AChE inhibition whereas the Day 2 rats from these dose groups exhibited 19-30% brain AChE inhibition.

The newly submitted statistical analysis now only uses the first analysis value thereby resolving the issue of the inconsistent inclusion/exclusion of data. By using the first values, the re-analysis issue does not affect the final interpretation. HED understands that in the laboratory there are occasions to re-analyze samples. HED encourages Gowan in the future to ensure that re-analysis procedures follow pre-determined criteria and that criteria are followed throughout the study. .

4. Study design

"The dose levels were selected based on the results from previous studies on the test material. No further details were provided in the report. Based on the fact that cholinesterase was to be monitored in three compartments for each sex and dose level, it is unfortunate that the registrant chose to use six dose levels rather than the usual three well-thought-out dose levels in this study. Given the fact that 60 mg/kg/day was a definite effect dose in the previous dermal toxicity study, based on brain cholinesterase inhibition in both sexes, the goal of the new study should have been on defining the NOAEL." [DER page 5]

- In what way is a 4-dose study superior to a 7-dose study when the intent is to determine dose response?
- As discussed in several submissions and meetings, a pilot experiment at CRL and also the previous MPI 21-day dermal study informed our study design and dose selection. All available information indicated strongly that the critical endpoint would be female RBC and that the NOAEL would be between 30 and 60 mg/kg/day. In what way was our decision to examine multiple doses between 30 and 60 mg/kg/day flawed?
- Is there a new policy rejecting block design studies and the routine statistics used to analyze these?

HED Response: HED understands that when conducting such a large study, dosing and sacrificing of animals must be staggered on different days. HED further notes that a 7-dose study conceptually would be superior to a 4-dose study in providing more data to determine a dose response, although the inclusion of additional dose groups introduces further challenges in study execution.

An important consideration in all studies is dose selection. When the goal is to determine a point of departure at or near 10% inhibition level for purposes of

extrapolating risk, the dose levels and dose spacing should be chosen such that the low-end of the dose-response curve is adequate to estimate this 10% level. During protocol review for the current dermal study, HED recommended to Gowan on multiple occasions that dose levels of 15 and 22.5 mg/kg/day be included (these dose levels represent the NOAEL and LOAEL from the MPI 21-day dermal study (1999) that were used in the previous October, 1999 risk assessment). Therefore, focusing on extra doses from 30 and 60 mg/kg/day missed the low end-end of the dose curve. As such, this study does not represent the low-end of the dose-response curve for phosmet.

5. Statistical report

"The fact that it took a 70-page statistical assessment of the results to reach a conclusion suggests a poor study design. Although the statistical procedures used are appropriate, the data analyzed by these statistical procedures are not considered reliable." **[DER page 5]**

- **In what way does a detailed and transparent statistical report, containing all data and methods used in the analysis suggest a poor study design?**

HED Response: HED would like to clarify the statement regarding study design. The intent of the statement was not meant to question the length of the report, but rather to convey HED's concerns about the reliability of the underlying data. HED encourages the use of quantitative analysis and appreciates the detailed, transparent nature of Gowan's statistical submission.

6. Combining data

HED has criticized combining the block replicates (Day 1 and Day 2) and Process 1 and Process 2 (Female RBC) data.

"Visually, it is apparent that there is a distinct difference between Day 1 and Day 2 for the females, with Day 2 showing higher levels than Day 1 across dose levels. For males, the three highest dose levels show lower values for Day 2 than for day 1. A statistical assessment of the data does not negate the fact that there is a difference between the two days and, for the female RBC data, between Process 1 and 2." **[DER page 19]**

- **Is it a new policy to reject statistical analyses in favor of visual impressions about data?**
- **At the chlorpyrifos SAP, HED combined male, female, acute and repeated dose data from different studies to derive endpoints. HED proposed similarly combining data from different studies at the carbofuran SAP. What are the criteria for combining data?**

HED Response: Regarding the comment of whether there is a new policy to reject statistical analyses in favor of visual impressions about data, the following table illustrates the meaning of the word "visually", as used in the DER. A clear difference is apparent between the values in the first three columns compared to the last column. All

of the values for Day 2 of the 120 mg/kg/day group are clearly below all of the control values for both Day 1 and Day 2 and for the Day 1 values of the 120 mg/kg/day group, suggesting a response on Day 2, but not on Day 1.

Table 3. Comparison of Individual Control and 120 mg/kg/day Male Brain ChE Values (U/g)			
Control		120 mg/kg/day	
Day 1	Day 2	Day 1	Day 2
13.962	12.899	12.810	10.317
14.183	14.489	13.078	9.989
14.963	14.838	13.540	10.366
13.422	15.739	14.559	10.120
14.060	-	14.767	9.569
13.136	-	-	-
13.136-14.963	12.899-15.739	12.810-14.767	9.569-10.366
13.954±0.638	**14.491 ±1.185**	**13.751±0.876**	**10.072±0.320**

HED encourages the use of quantitative tools for evaluating toxicology data. The use of statistical and empirical tools improves the overall analysis. Furthermore, HED has no concerns with how the statistical analysis was done. However, although a defined set of criteria have not been established for combining data, the underlying assumption is that the data sets are of sufficient quality to allow the statistical analysis to be meaningful. Because of the concerns with the conduct of the study, particularly the lack of established criteria for reanalysis of samples and the apparent differences between the Day 1 and Day 2 results, concern exists that using the combined data may not be health protective. HED routinely considers both biological and statistical considerations when making determinations of appropriate endpoints for risk assessment, and both are considered important when determining whether or not it is appropriate to combine data. HED's evaluation of both biological and statistical considerations is consistent with the Agency's Benchmark Dose Guidance (USEPA, 2000) which states "Data sets that are statistically and biologically compatible may be combined....." In this case, the weight of evidence considering the results of both this study as discussed, as well as the results of other toxicity studies in the database, indicates that consideration of the data from the two days separately is not unreasonable and is necessary to assure appropriate health protection.

ATTACHMENT A

1. Number of re-assays performed on Day 1 verses Day 2

At the October 29, 2008 meeting, HED pointed out the fact that more re-assays (*i e.*, quality control assays) were performed on Day 2, which suggested to HED that something was different on Day 2. HED appreciates Gowan's responsiveness to this issue. Inconsistencies in reanalyses have been the subject of multiple submissions by Gowan and meetings between Gowan and HED. The explanation provided in the November 6, 2008 email confirms HED's conclusion; namely, that the samples from Day 1 and Day 2 were not handled in a similar manner.

2. Variability in male brain ChE response

The fact that the 120 mg/kg/day male brain ChE results will not drive the overall study endpoint or risk assessment, as noted by Gowan, is not germane to the discussion of the noted difference in the male brain ChE response between Day 1 and Day 2. The real issue, to reiterate, is the lack of replicability. The issue remains; there is a qualitative and biologically meaningful difference in the results between the two days. Specifically, in Day 1 animals, no brain inhibition was observed but in Day 2 animals 30% was observed. As can be seen in the table below, the male 120 mg/kg/day Day 1 brain ChE values are within those of the Day 1 and Day 2 control brain ChE values. ALL of the 120 mg/kg/day Day 2 male brain ChE values are well below all of the control values of both days and those of the 120 mg/kg/day males on Day 1 (Table 1).

Table 1. Comparison of Individual Control and 120 mg/kg/day Male Brain ChE Values (U/g)

Control		120 mg/kg/day	
Day 1	**Day 2**	**Day 1**	**Day 2**
13.962	12.899	12.810	10.317
14.183	14.489	13.078	9.989
14.963	14.838	13.540	10.366
13.422	15.739	14.559	10.120
14.060	-	14.767	9.569
13.136	-	-	-
13.136-14.963	12.899-15.739	12.810-14.767	9.569-10.366
13.954±0.638	**14.491 ±1.185**	**13.751±0.876**	**10.072±0.320**

3. Variability on Process 1 verses Process 2 Female RBC

With regard to the issue that HED is basing conclusions on "selected" examples, the samples identified were to demonstrate the problem noted (assay of same sample did not replicate). The selected examples were not unique..

4. Weight-of-the-evidence determination of dermal endpoint

Gowan agrees with the Agency that a weight-of-the-evidence approach is appropriate for determining the dermal rat point of departure. However, HED disagrees with the endpoint selected by Gowan (NOAEL of 30 mg/kg/day for female RBC).

When Day 1 and Day 2 results from the 2007 CRL study are considered separately, HED notes that in the 30 mg/kg/day group 14-23% RBC AChE inhibition was observed in Day 2 females. This observation is similar to results of the 1999 MPI dermal toxicity study where female brain AChE was observed at 22.5 mg/kg/day (13-20%) (Table 2). Moreover, both dermal studies provide similar results to using the subchronic neurotoxicity oral study where a $BMDL_{10}$ of 1.0 mg/kg/day was estimated for RBC ChE inhibition (following adjustment using the dermal absorption factor of 10%).

Table 2. Rat studies available for use in determining the dermal point of departure.

Study	CRL (2007) MRID 47262502	MPI (1999) MRID 44795801	WIL (1999) MRID 44811801
Study type	21 day dermal	21 day dermal	90 day oral
Doses (mg/kg/day)	30, 40, 50, 60, 90, 120	15, 22.5, 60	1.5/1.6; 2.7/3.1; 9.4/11.0
Rat strain	Crl:CD(SD)	Sprague-Dawley (Crl:CD VAF/Plus)	Crl:CD(SD)IGS BR
Endpoint	Female RBC	Female brain	RBC (♀ and ♂)
NOAEL (mg/kg/day)	<30	15	<1.5/1.6
LOAEL (mg/kg/day)	30	22.5	1.5/1.6
% RBC ChEI @ LOAEL	♀ 14-23% (Day 2)	14% (not reliable)	♂ @ week 3 (13%)
% brain ChEI	Day 2 ♂ (10, 14, 19, 30% @ 50, 60, 90, 120)	@ 60 ♀ (61/53%)/♂ (36/25%) @ 22.5 ♀ (20/13%)	11% week 3 ♂ @ 2.7 BMD/BMDL 2.79/2.22
BMD_{10}	-	-	RBC (♀♂) 1.949
$BMDL_{10}$	-	-	1.036
Strengths	Appropriate route of exposure 6 dose groups/both sexes	Appropriate route of exposure 3 dose groups/both sexes	dose-response data for BMD analysis
Weaknesses	Replicability and re-analysis issues	Assay issues w/ RBC	Oral study
POD	<30	15	10

% inhibition compared to concurrent/expanded control

Each of the three studies in Table 2 has some uncertainty associated with it for use in risk assessment. For example, the 1999 MPI dermal study used a non-validated ChE assay but demonstrated a NOAEL of 15 mg/kg and LOAEL of 22.5 mg/kg based on female brain ChE inhibition. Although the method used in the MPI study was not cross-validated for rat tissues, HED considers the brain data to be of sufficient quality for risk assessment since brain AChE activity tends to be high. However, HED does not have confidence in the RBC data from this study. Therefore, the LOAEL of 22.5 mg/kg can not be discounted.

As annotated in the memo responding to the October, 2008 letter, HED has concerns with the 2007 CRL dermal study with regard to the replicability of samples (Process 1 and Process 2) as well differences in inhibition based on the day of analysis (Day 1 vs. Day

2). Finally, the oral study (WIL 1999) demonstrates a $BMDL_{10}$ of 1.0 mg/kg/day (3-week assessment) but is not route specific data. EPA typically tries to incorporate route specific data into risk assessments.

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