MICROFICHE

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

013722

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

May 5, 1999

SUBJECT: Review of the Histopathology Assessment of Nasal Tissues for the Malathion 18-Month Oral (Dietary) Carcinogenicity Study in Mice (MRID: 44733501; 44792301)

FROM: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 5/5/99
Toxicology Branch 1
Health Effects Division (7509C)

THRU: Alberto Protzel, Ph.D. Alberto Protzel 5/5/99
Senior Branch Scientist
Toxicology Branch I
Health Effects Division (7509C)

TO: Phillip Poli
PM Team 53
Special Review and Reregistration Division (7508W)

Registrant: Cheminova Agro A/S
Chemical: Malathion
Case No.: 818961
DP Barcode: D252655
MRID Nos.: 44733501; 44792301

Submission No.: S555503
PC Code: 057701

ACTION: Expedited Review, 6(a)(2) data. Review the peer reviewed histopathology assessment of nasal tissues for the malathion 18-month carcinogenicity study in the mouse. This assessment of nasal tissues of the previously submitted and reviewed carcinogenicity study was requested by the September/October 1997 meeting of the Cancer Assessment Review Committee (CARC) to consider the malathion data base. Nasal tissues were not examined histopathologically in the original study submission (MRID 43407201).

1

CONCLUSION:

Presented below are the Citation and Executive Summary of the reviewed study; the Review follows.

CITATION:
An 18-month Oral (Dietary) Oncogenicity Study in Mice. Test Substance: Malathion. Author: Richard W. Slauter, Ph.D., October 12, 1994. Performing Laboratory: International Research and Development Corporation, Mattawan, Michigan. Sponsor: Cheminova Agro A/S, Lemvig, Denmark. (MRID 43407201)

An 18-month Oral (Dietary) Oncogenicity Study of Malathion in Mice: Nasal Tissue Evaluation and Peer review. Author: James A. Swenberg, D.V.M., Ph.D., January 8, 1999. Sponsor: Cheminova Agro A/S, Lemvig, Denmark. (MRID 44733501)

An 18-month Oral (Dietary) Oncogenicity Study of Malathion in Mice: Nasal tissue Evaluation and Peer Review. Author: James A. Swenberg, D.V.M., Ph.D. January 8, 1999. Sponsor: Cheminova Agro A/S, Lemvig, Denmark. PQA Review Summary Table (MRID 44792301).

EXECUTIVE SUMMARY:

Toward fulfilling a requirement of HED's CARC for the histopathology evaluation and peer review of microscopic slides of nasal tissues among mice of both sexes in the malathion Carcinogenicity Study in B6C3F1 mice (MRID 43407201), the sponsor has submitted the results of this peer review. In that Guideline study, B6C3F1 mice of both sexes were administered malathion via the diet for a period of 18 months at dietary concentrations of 0, 100, 800, 8000 and 16000 ppm (equivalent to 0, 17.4, 143, 1476 and 2978 mg/kg/day in males and 0, 20.8, 167, 1707 and 3448 mg/kg/day in females). Standard Guideline testing procedures were followed. Nasal tissues were not examined microscopically in the original study submission. This follow-up submission reports the histopathologic findings for all mice as derived from microscopic examinations of nasal tissue sections taken from five nasal regions, denoted in the study report as tissue sections A through E, for each mouse. This involved both independent assessments by the Study Pathologist and the Reviewing Pathologist, who subsequently met to arrive at consensus diasgnoses for all slides wherein differencies of opinion existed.

There were no *neoplastic findings* interpreted as related to treatment. There were four neoplasms identified in the study. These included a peridontal hemangiosarcoma in one control male (animal 48891), an odontoma in another control male (animal 48905) and an odontoma in each of two male mice in the low dose group (animals 49030 and 49039).

Treatment-related *non-neoplastic toxicologic findings* of increased incidence observed in ***mice of both sexes*** at 8000 and 16000 ppm were: "exudate, suppurative", "increased glandular secretion", "olfactory degeneration", "olfactory atrophy" and "olfactory respiratory metaplasia".

Increased incidences of "hyperplasia of Bowman's gland" were seen at 8000 and 16000 ppm in males, but only at 16000 ppm in females. Among ***male mice***, "olfactory degeneration", "olfactory atrophy", "olfactory respiratory metaplasia" and "hyperplasia of Bowman' gland" were essentially clear cut as observed at the top two doses, but not at the lower doses or control. In males there was some slight evidence of increased incidence of "exudate, suppurative" and "increased glandular secretion" at the lower doses, which must be considered equivocal. Among ***female mice***, all of the parameters identified as increased at 8000 ppm, with the exception of "olfactory respiratory metaplasia", clearly extended to the 800 ppm dose level. "Olfactory degeneration" and "olfactory atrophy" are end points of particular toxicologic concern among females at 800 ppm. A matter of further concern is whether "olfactory atrophy" extended to the lowest dose group, 100 ppm, in this study. Accordingly, there were three female mice in the low dose group exhibiting this effect, described in each case as "mild", while by contrast in the control group there was but one finding of "olfactory atrophy", described as "trace". It is important to note that "olfactory atrophy", where seen in both sexes, predominated in nasal tissue sections D and E, which were the loci of the control and low dose group findings. Among females at 800 ppm the incidences of this finding were numerous in tissue sections D and E.

Hence, for *neoplastic findings*, there were none interpreted as related to treatment. For *non-neoplastic* nasal tissue pathology, for males NOAEL/LOAEL = 800/8000 ppm ; for females NOAEL/LOAEL = 100/800 ppm (certain), or NOAEL/LOAEL = < 100/100 ppm (equivocal). The final designation of NOAEL/LOAEL for the study is deferred to the Cancer Assessment Review Committee.

This study is **ACCEPTABLE/NON-GUIDELINE.** This is a special study not designed to satisfy a Guideline requirement. The study did clearly not identify a NOAEL for female mice.

The following are noteworthy: a) This was an oral feeding study, and it is uncertain whether the nasal tissue exposure was entirely systemic or partially via the inhalational route. However, there was little or no reported evidence of food debris in nasal passages that would support an inhalational route of exposure, nor was any claim made by the pathologists that a component of exposure was via the nasal route in this mouse study. As with all liquids, malathion has a vapor pressure, but whether it is a significant contributor to exposure via evaporation from the feed is inestimable, but considered likely to be only a relatively minor contributor to exposure.; b) There is considerable uncertainty as to what the effects on nasal tissues would be via inhalation treatment, particularly at malathion concentrations yielding systemic effects (e.g. plasma or erythrocyte cholinesterase inhibition) equivalent to those seen in this oral feeding study; c) This was an 18 month (78 week) study. In view of the considerable nasal tissue pathology, the study may be deficient for nasal tissue carcinogenicity assessment in not having been conducted for a full two years. Since the 1978 NCI study, performed in the B6C3F1 mouse at 0, 8000 and 16000 ppm, was an 80 week treatment, but 95 week in-life study, one may speculate that with an additional 17 week period, progression to neoplasia might be observable. The question of whether nasal tissues from that study should be examined histopathologically, if possible, will be considered by the HED Cancer Assessment Review Committee (CARC).

The HIARC at its last assessment of malathion required another inhalation study in the rat. Nasal tissue findings in this mouse study as well as in the other Guideline studies should be taken into consideration in the design of the new inhalation study. Furthermore, all studies, both inhalation and chronic studies on malathion must ultimately be assessed concertedly in characterizing nasal tissue responses to the test material before definitive conclusion can be drawn as to the nasal toxicity of this material.

REVIEW OF PATHOLOGY WORKING GROUP REPORT

I. BACKGROUND

The HED Carcinogen Assessment Review Committee (CARC) convened during September and October 1997 to consider the malathion cancer assessment data base elected to require the histopathologic examination and peer review of microscopic slides of nasal tissues among mice of both sexes in the mouse carcinogenicity study (MRID 43407201). Nasal tissues were not so examined in the original study submission. This requirement, along with others from the CARC, was recorded in a November 3, 1997 report by Jess Rowland, Executive Secretary, CARC "Malathion: request for reevaluation of tissues/slides by the Cancer Assessment Review Committee (HED Report No. 012374)." These requirements were in turn forwarded to the registrant's sponsor via a January 7, 1998 letter of Walter Waldrop, Chief, Registration Branch III, SRRD. The results of the histopathology examination and peer review of the mouse nasal tissue component of the data requirements has now been submitted to the Agency (MRID 44733501; 44792301), and is the subject of this review.

According to this submission, the report contains the results of the evaluation and peer review of the mouse nasal tissues that were conducted according to PR Notice 94-5 in response to the January 7, 1998 letter from Walter Waldrop, as mentioned above. Furthermore, the report claims the data are being submitted "....under Section 6(a)(2) because it contains the results of pathology evaluations of tissues not previously evaluated in the original mouse oncogenicity study (MRID 43407201) that was conducted at MPI Research (MPI)." (From the 1/12/99 letter of Blane Dahl, Jellinek, Schwartz and Connolly, Inc. to Ms. Dana Lateulere, Office of Pesticide Programs, USEPA).

Further, according to the sponsor's January 12 letter, MPI prepared five sections of nasal tissues from all mice in the original mouse oncogenicity study. According to the study report itself, MPI study pathologist, Dr. Daniel Rajasekaran, performed the initial histopathology readings, while Dr. James Swenberg served as peer reviewing pathologist.

II. THE STUDY REPORT

i) Review Procedure

As set forth in the January 12, 1998 letter of Walter Waldrop five nasal tissue sections were

required by the Agency, to be taken as described in the Journal Publication, Eldridge, S.R., et al (1995) Fund. Appl. Toxicol. 27, 25-32. Furthermore, the agency specified the evaluations to be done in compliance with the August 24, 1994 PR Notice 94-5, although the PWG component of the PR Notice was not applicable to the data requirement, i.e., in the case of the nasal tissue histopathology requirement, the Agency was not seeking a Pathology Working Group (PWG). Rather, the Agency was seeking an initial assessment by a designated Study Pathologist followed by an assessment by a Reviewing Pathologist.

As conducted by this peer review process, the Study Pathologist, Dr. Rajasekaran, initially read each slide histopathologically, and prepared a report which, along with the slides was provided to the Reviewing Pathologist, Dr. Swenberg, who in turn interpreted each slide. The individual diagnoses rendered by each pathologist in addition to a consensus diagnosis are recorded in the study submission. Upon receipt of this report, HED's Reviewing toxicologist (Dr. Dementi) requested the sponsor to provide a summary table of the findings, as such a tabulation of the data was not provided in the original submission. The summary table was subsequently submitted via a February 17, 1999 letter of Paul Whatling of Jellinnek, Schwartz and Connolly. (MRID 44792301)

ii. HED'S Review of Submission

Appended is a copy of the Summary Table of histopathology findings (Attachment No. 1) taken from the study submission (MRID 44792301). Also included as a component of this review is a tabulation of selected end points, taken from the Summary Table, designed to facilitate the discussion. Histopathologic findings are recorded in these tables for each of the five nasal tissue sections (A through E) taken. Both interim sacrifice and terminal sacrifice findings are recorded in the Summary Table, while only terminal sacrifice data is included the tabulation of selected end points prepared for this review.

a) *Neoplastic Findings:* An inspection of the Individual Animal Data and the Summary Table disclose that neoplastic findings were limited to the following: a peridontal hemangiosarcoma in nasal sections B through E of a control male mouse (# 48891), an odontoma in sections B through D of a control male (# 48905), an odontoma in section C of a low dose male (# 49030) and an odontoma in sections C and D of another low dose male (# 49039). It should be noted that while all four of these lesions were accounted for in both the Individual Data and Summary Table data sheets for the mice in question, the findings in the low dose male group were not acknowledged in the Reviewing Pathologist's January 8 Narrative Summary, which says "Only two neoplasms were found in the study, a hemangiosarcoma surrounding a tooth in a control male and an odontoma in another control male." (p. 9 of the study submission). The same mistaken characterization of tumor incidence appears in the January 12, 1999 letter of the registrant's representative, Blane Dahl to Ms. Dana Lateulere (p. 2). **These two documents should be corrected for the sake of the accuracy of the written record.** There were no other tumors identified beyond the four as indicated above.

b) *Non-neoplastic findings:*

1) **Reviewing Pathologist's Assessment of Results.**

In his Narrative Summary, the Reviewing Pathologist describes the non-neoplastic findings as follows. "The results of this pathology peer review found a discrepancy between the Study Pathologist and the Peer Review Pathologist. Whereas the Study Pathologist identified 'Increased Nasal Secretion' in the nasal turbinates of many of the mice in Groups IV and V, little (other) pathology was identified in the original examination. In addition, Dr. Swenberg found extensive olfactory toxicity in most mice in Groups IV and V.

"In the interim sacrifice animals (Appendix A), the olfactory toxicity was characterized by degeneration with loss of cellularity of the olfactory epithelium and *loss of olfactory nerves in the submucosa* (emphasis added), increased glandular secretion in the lumen due to retention of mucus, and *atrophy of the olfactory epithelium*(emphasis added) adjacent to retained mucus. Some of the mice in Group III also showed increased glandular secretion. The olfactory degeneration was of greatest severity and incidence in the dorsal meatus of sections B, C, and D. Male and female mice responded similarly.

"Mice from the terminal sacrifice and those that died or were killed after the interim sacrifice (Appendix B) exhibited similar lesions to those exposed to Malathion for 12 months or less. In addition, respiratory metaplasia was often present in regions of olfactory mucosa with more extensive degeneration, such as in the dorsal meatus of sections B, C, and D. In regions where the olfactory degeneration was moderate to severe, hyperplasia of Bowman's glands was also evident in many animals. Inflammation and the presence of suppurative exudate was increased in mice exposed to Groups III, IV, and V in a dose-related manner." (pp. 8-9 of the Study Report) The Reviewing Pathologist did not attempt to identify the LOAEL/NOAEL for the study.

2) **HED's Review of the Submission.**

Inspection of the individual terminal sacrifice animal data discloses a remarkable disparity between the assessments of the Study Pathologist and Reviewing Pathologist, which was settled in the form of a consensus rendering of interpretation between the two, with essentially complete affirmation of those diagnoses first provided by the Reviewing Pathologist. The Reviewing Pathologist identified (and later obtained concurrence of the Study Pathologist) the following among ***female mice*** (see the incorporated Tabulation of Selected Findings from MRID 44792301): high incidences of olfactory atrophy (Groups 3, 4 and 5, essentially confined to tissue sections D and E), olfactory degeneration (Groups 4 and 5, sections B thru E) and olfactory respiratory metaplasia (Groups 4 and 5; sections B thru E). In addition, both pathologist shared original diagnoses of increased incidences of "Exudate, Suppurative" (Groups 3, 4 and 5; most pronounced in sections A, B and D); and "increased glandular secretion" (Groups 3, 4 and 5; tissue sections B thru E). Hyperplasia of Bowman's gland was elevated only in Group 5, primarily in tissue section D.

Among ***male mice,*** olfactory degeneration and olfactory atrophy were first reported by the Reviewing Pathologist and later concurred in by the Study Pathologist as of high incidence in Groups 4 and 5. Olfactory degeneration (see the Tabulation of Selected Findings from MRID 44792301) was seen in tissue sections B thru E and olfactory atrophy primarily in sections D and E, as was true of the location in females. Similarly, the Reviewing Pathologist identified increased incidences of "hyperplasia of Bowman's Gland" (Groups 4 and 5, particularly in section D, and to lesser incidences in sections C and E). In addition, both pathologists identified and subsequently concurred in diagnoses of high incidences of "increased glandular secretion" (Groups 4 and 5, particularly in section D, but also in sections C and E).

Thus there is clear evidence of nasal cavity toxicity at the 8000 and 16000 ppm dose levels in both sexes and in females at 800 ppm as well. An important question is whether a NOEL has been identified in this study for non-neoplastic histopathology. Findings among male mice at terminal sacrifice do not support an effect at the 100 or 800 ppm dose levels. Among females, incidence of olfactory atrophy, which was increased at 800, 8000 and 16000 ppm in a dose related manner in tissue sections D and E, may also be an effect at 100 ppm. In the 100 ppm group, there were three females (I.D. #s 49064, 49087 and 49089) with olfactory atrophy described in all cases as "mild". One of these was in section D and two in section E. There was one control female (I.D. # 48951) with the same effect identified in tissue section D, described as "trace". The facts that this effect was more severe in the three low dose animals affected than in the case of the single control incident, and was dose related across the top three doses in both sections D and E, are supportive of a positive effect at 100 ppm as described. However, the incidence at 100 ppm (5.5%) was low, and substantially less than in the top three doses.

At the interim sacrifice (MRID 44792301), there was evidence of nasal toxicity among males and females at 8000 and 16000 ppm in terms of olfactory degeneration and atrophy. There was little effect among males at the two lower dose levels, but in females at 800 ppm, six of the eleven rats examined exhibited increased glandular secretion and two exhibited olfactory atrophy, and in the 100 ppm group three of the ten examined had increased glandular secretion, with no other findings. There were no findings among the ten interim sacrificed control females. The findings in females at 800 and 100 ppm, which appear to be dosing related and having occurred by the time of interim sacrifice, serve to support the findings among females at 100 ppm evident at terminal sacrifice as related to treatment.

In summary, for non-neoplastic nasal toxicity, among male mice, the LOAEL = 8000 ppm; NOAEL = 800 ppm; while in females LOAEL = 800 ppm (certain)/100 ppm (equivocal); NOAEL $\leq$ 100 ppm. It is noteworthy that the Reviewing Pathologist did not venture to assign a NOAEL/LOAEL to this study. There remains the need to identify a definitive NOAEL among females and to determine the time of onset of nasal pathology.

3) **DISCUSSION**

In terms of carcinogenicity, there were but four neoplastic lesions in the study. A

hemangiosarcoma in one male control and an odontoma in another male control, while an odontoma was also identified in each of two low dose group males. As a point of fact, odontoma is defined in Taber's Cyclopedic Medical Dictionary, 14th Edition as "tumor of a tooth or tumor originating in the dental tissue." According to this reference there are different types of odontomas: "coronary", "follicular" and "radicular". Odontomas are to be described as tumors of the tooth proper. The two mice with odontoma in the low dose group versus the one in the control, standing alone cannot be interpreted as evidence of carcinogenicity. *In view of the extensive nasal toxicity in this 18 month (78 week) study, there should be an inquiry to determine whether nasal tissues were, or could be, examined in the 1978 NCI study (Carcinogenesis Technical Report Series No. 24), particularly since this study was conducted for 95 weeks in-life, and would have afforded greater opportunity for the nasal effects to become fully expressed, possibly to the point of neoplasia.*

From a review of the non-neoplastic data, and the assessment of the Reviewing Pathologist, it is noteworthy that mice fed malathion in the diet exhibit extensive nasal toxicity that was evident at the *interim sacrifice*. We have no indication from this study how soon the effects would first be observed in terms of both dose and time of onset. Olfactory atrophy and degeneration accompanied by the *loss of olfactory nerves* must be viewed as serious toxicologic effects. Olfactory atrophy was clearly evident at a lower dose level in females. The Reviewing Pathologist says that males and females were similarly affected at the interim sacrifice, but neglected to note that at term females clearly exhibited enhanced incidence of olfactory atrophy at 800 ppm, an effect not observed in males at this dose, and that an equivocal finding for this effect among females resides at 100 ppm, the lowest dose level. We have no explanation for the greater sensitivity of females. It is probably contributed to but not adequately explained by the greater test compound intake among females as expressed on a mg/kg bodyweight basis, and perhaps is related to the more remarkable cholinesterase inhibition seen among females as presented in the full review of this carcinogenicity study.

The findings is this study cannot be viewed in isolation, but must be considered in concert with the other malathion studies where nasal toxicity has been observed. The studies include the combined chronic toxicity/carcinogenicity studies of both malathion (MRID 43942901) and malaoxon (MRID 43975201) in the F344 rat, the subchronic inhalation study in the Sprague-Dawley rat (MRID 43266601), and the 2-week range-finding inhalation study in Sprague-Dawley rats (MRID 44554301) performed for dose selection in the subchronic inhalation study. Furthermore, it would seem appropriate to inquire of NTP as to what information might be available concerning nasal tissue effects in the various NCI studies conducted in the 1978-80 period. The Agency is requiring a new inhalation study as a result of deliberations during the 1998 HIARC meetings on malathion. The conduct of this study should be very carefully planned in order to be certain to address the potential for nasal toxicity.

While dosing in this study was oral, we cannot be certain that at least part of the exposure was by the inhalational route. Yet, the reviewing pathologist has made no claim to this effect nor cited any evidence, such as food residues in the nasal cavity, that might support nasal exposure by the

direct inhalational route. So to the extent that the effects seen on the nasal mucosa were systemic following oral ingestion, there is opportunity for speculation that nasal effects via the inhalational route wherein there is direct contact with the nasal mucosa, may be of enhanced or unaddressed concern. This begs for definitive inhalation studies.

It would be important to assess comparative metabolic capabilities of rat and mouse nasal tissues in assessing responses in both species. Again, more will need to be said, in another document, about the concerted nasal tissue findings in various in-house studies, both by the oral and inhalational routes.

TABULATION OF SELECTED FINDINGS
CONSOLIDATED FROM THE STUDY REPORT PQA REVIEW SUMMARY
(Terminal Sacrifice)

Tissues: Nasal (Sections A thru E)					
FEMALES **Dietary Conc. (ppm.)** **No. Animals Examined**	0 55	100 55	800 54	8000 53	16000 52
Exudate, Suppurative					
A	0	0	9	15	19
B	0	2	2	9	10
C	0	0	0	3	3
D	0	0	1	4	8
E	0	0	0	1	3
Increased Glandular Secretion					
A (N/A)					
B	0	0	8	9	5
C	3	1	17	45	29
D	2	3	37	52	50
E	2	2	27	43	49

9

Olfactory Degeneration					
A (N/A)					
B	0	0	5	47	46
C	0	0	2	52	50
D	0	0	3	53	51
E	0	0	0	35	44
Olfactory Atrophy					
A (N/A)					
B (N/A)					
C	0	0	1	0	1
D	1(trace)	1	26	38	29
E	0	2	21	33	37
Olfactory Respiratory Metaplasia					
A (N/A)					
B	0	0	0	28	34
C	0	0	1	31	18
D	0	0	0	46	19
E	0	0	0	21	15
Hyperplasia of Bowman's Gland					
A (N/A)					
B (N/A)					
C	0	0	0	0	5
D	0	0	0	0	22
E	0	0	0	0	5

MALES (No. Ex.)	(54)	(55)	(55)	(55)	(51)
Exudate, Suppurative					
A	1	4	2	13	10
B	1	3	2	8	12
C	1	0	1	4	4
D	0	0	0	3	7
E	0	0	0	3	2
Increased Glandular Secretion					
A	0	0	0	0	1
B	0	0	0	3	5
C	0	1	1	27	28
D	0	2	2	51	45
E	0	2	1	35	29
Olfactory Degeneration					
A	N/A				
B	0	0	0	39	31
C	0	0	0	53	44
D	0	0	0	55	47
E	0	0	0	36	37
Olfactory Atrophy					
A (N/A)					

B (N/A)					
C	0	0	0	0	3
D	0	0	0	30	23
E	0	0	0	28	20
Olfactory Respiratory Metaplasia					
A N/A					
B N/A					
C	0	0	0	3	8
D	1	0	0	15	17
E	0	0	0	6	3
Hyperplasia of Bowman's Gland					
A N/A					
B	0	0	0	0	1
C	0	0	0	11	12
D	0	0	0	31	30
E	0	0	0	17	11

The following attached document (**MRID 44792301**), entitled "Summary of an 18-month Oral (Dietary) Oncogenicity Study Of Malathion in Mice: Nasal Tissue Evaluation and Peer Review-MRID 4473350", is not available electronically.

See the file copy for hard copy of the attachment.

13

RIN0004-01

Box R 013722

Page _____ is not included in this copy.

Pages 14 through 25 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.