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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

August 24, 2010

**MEMORANDUM**

**Subject:** Occupational and Residential Exposure and Risk Assessment for the New Active Ingredient N, N-Methylenebismorpholine (Contram ST-1, 52484-G)

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**To:** Dennis Edwards, Chief
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Regulatory Management Branch I
Antimicrobials Division (7510P)

**Barcode:** D358622

**Chemical:** N,N-Methylenebismorpholine (Cas 5625-90-1)

**PC Code:** 054702

**Registrant:** The Lubrizol Corporation

## 1.0 Action Requested

The Antimicrobial Division's (AD) Regulatory Management Branch I has requested that the Risk Assessment and Science Support Branch (RASSB) conduct exposure and risk assessments to support Lubrizol's application for registration of Contram ST-1, which contains a new active ingredient N,N-Methylenebismorpholine (MBM). RASSB was also requested to review a worker exposure study (MRID 475558-31, UK Exposure Study) that was submitted by Lubrizol to support this registration.

## 2.0 Summary of Findings

The submitted data in conjunction with the data available from the literature appears to suggest that formaldehyde exposures from the use of Contram ST-1 in metal working fluids (MWF) will not exceed the EPA level of concern of 100 ppb. However, this preliminary conclusion is based on the assumption that the Lubrizol study was conducted under typical machine shop conditions. It is recommended that additional formaldehyde samples be collected in a several additional machine shops to verify the extremely low levels of formaldehyde measured during the Lubrizol study. These samples should be collected using sampling times of 10-15 minutes each so that results will be comparable to the LOC of 100 ppb which is a peak value. A protocol should be submitted to EPA for review prior to the initiation of the study.

If additional sampling indicates that formaldehyde exposures exceed the LOC under typical machine shop conditions, then engineering controls such as machine enclosures and local exhaust ventilation will be required. It will also be necessary to collect additional sampling to verify the performance of the machine enclosures because such systems were often designed for the control of oil mist and were not intended to control formaldehyde vapors. This is particularly true for machine enclosures connected to mist elimination systems where the air is recirculated back into the work area after passing through a filtration unit. While such systems can be effective for trapping aerosols that consist of oil mist and typical biocides that are essentially non-volatile, these systems are not effective for volatile biocides such as formaldehyde unless they are vented to the outside.

## 3.0 Product Use Profile

Contram ST-1 is a formaldehyde releasing preservative that contains a new active ingredient, MBM (purity of 98.5% a.i., 14 to 16% available formaldehyde). It is proposed for use as a preservative to control non-public health bacteria and some fungi in MWF. It is intended to be distributed to mixers of MWF concentrates and will be added to these concentrates at a rate of approximately 3.0 percent. The concentrate, which is considered to be a treated article, will then be sold to machine shops and diluted on site to a maximum end use concentration of 2000 ppm Contram ST-1 or 300 ppm free formaldehyde.

## 4.0 Summary of Toxicological Endpoints

MBM Acute Toxicity

Three of the six required acute toxicity studies have been submitted for MBM and their results are summarized in Table 1.

**Table 1 - Acute Toxicity Values for MBM**

| MRID | Test (species) | Result | Toxicity Category |
|---|---|---|---|
| 475713-02 | Oral Toxicity (rat) | LD50 - >500, <2000 mg/kg/day | III |
| No study submitted | Dermal Toxicity (rabbit) | N/A | N/A |
| No study submitted | Inhalation Toxicity (rat) | N/A | N/A |
| No study submitted | Eye Irritation (rabbit) | N/A | N/A |
| 475713-03 | Skin Irritation (rabbit) | Corrosive | I |
| 475713-04 | Dermal sensitization (guinea pig) | Not a Dermal sensitizer | N/A |

MBM Subchronic/Chronic Toxicity

The two submitted studies for subchronic/chronic toxicity are included in Table 2. Both of these studies involved oral dosing, however, and are not relevant for the assessment of the proposed MWF use because MWF exposures occur primary via the dermal and inhalation routes. For this reason and because MBM releases formaldehyde, endpoints for the assessment of the parent MBM dermal and inhalation exposures were not selected. Instead, the risk assessment of the proposed use was based on formaldehyde endpoints as discussed in the formaldehyde toxicity section below.

**Table 2 - Toxicology Profile for N,N-Methylenebismorpholine (MBM)**

| Study | Doses Tested (mg/kg/day) | NOAEL (mg/kg/day) | Toxicological Effects |
|---|---|---|---|
| Oral Prenatal Developmental -Rabbit (475713-07) | 0, 10, 30, 100 | 10 (maternal) 100 (developmental) | Maternal – treatment related stomach effects including erosion and granular aspect was observed at the LOAEL of 30 mg/kg/day. Developmental – no effects were observed at the highest dose tested. |
| 90 day Oral Toxicity, Gavage – Rat (475713-05) (475713-06) | 0, 5, 15, 50, 250/150 | 15 | Microscopic changes to the non-glandular stomach were observed at the LOAEL of 50 mg/kg/day. |

Formaldehyde Toxicity

Table 3 summarizes the toxicological endpoints for formaldehyde which are described in more detail in following memorandum: "*Formaldehyde/Paraformaldehyde - Report of the Antimicrobials Division Toxicity Endpoint Selection Committee (ADTC)*" from T. McMahon to S. Carlisle, dated June 24, 2008. Endpoints were selected only for assessing inhalation exposures to formaldehyde and it was determined that assessments of the other routes of exposure (dietary, dermal and incidental oral) would not be not required.

In addition, the following disclaimer from the "*Response to Public Comments on the Formaldehyde Preliminary Risk Assessment RED" from T. McMahon and T. Dole to S. Carlisle, dated January, 6, 2009* is provided for the non-cancer formaldehyde inhalation endpoint:

*OPP developed the formaldehyde inhalation non-cancer toxicological endpoint used in this document through the established registration process, which includes stakeholder consultation and public comment. However, the result has not been subjected to an inter-agency review or external peer review. Because of time constraints imposed by statutory deadline, OPP could not consider all available peer reviewed science (for example, the intentional human dosing toxicity studies). Thus, this value should be considered an interim value, developed solely for the purposes of this determination and subject to future revision and subsequent peer review and should not be used in other contexts as EPA's opinion of the best available science on the non-cancer effects of formaldehyde.*

For the purposes of this assessment, the formaldehyde endpoints are expressed as RfCs which are the NOAEL divided by the uncertainty factor (UF). The UF is 1 for the occupational exposures because the NOAEL was derived from observational studies of workers exposed to formaldehyde and the UF is 10 for the residential exposures to account for the increased sensitivity of some members of the residential population. It is also important to note these RfCs are for peak exposures.

**Table 3 - Summary of Toxicological Doses and Endpoint Selection for Formaldehyde**

| Exposure Scenario | Dose Used in Risk Assessment | Reference Concentration (RfC) | Study and Toxicological Effects |
|---|---|---|---|
| **Inhalation** (all durations) | NOAEL (human) = 100 ppb | $RfC_{occupational}$ = 100 ppb<br>$RfC_{residential}$ = 10 ppb<br><br>Where:<br>RfC = NOAEL / UF<br>UF = 1 for occupational<br>UF = 10 for residential | ACGIH 2001, TLV Documentation for Formaldehyde<br><br>Horvath, E.P. et al. (1986): JAMA 259(5): 701-707. Based on complaints of eye, nose, and throat irritation in particle board workers at concentrations of formaldehyde from 0.4 – 1.0 ppm.<br><br>Redden, J. (2005): Section 18 Emergency Exemption for the use of Paraformaldehyde: U.S. Army Medical Research Institute of Infectious Diseases. |
| **Cancer** | **Lifetime extra cancer unit risk estimate of 1.3 × $10^{-5}$ per μg/m³** (US EPA IRIS http://www.epa.gov/ncea/iris/subst/0419.htm)<br><br>And<br><br>**CIIT modeling**: Tables 8A (for residential) and B (for professional). Hockey stick-shaped CRCP (nonsmoking) (Conolly, 2004) | | |

## 5.0 Exposure Assessment

Occupational dermal and inhalation exposures to MBM can occur during the use of MWFs containing Contram ST-1. Mixer/Loader exposures will occur during the mixing of the MWF concentrate that contains 3 percent MBM with dilutants to produce the end use fluid and machinist exposures will occur while using the end us fluid for machining.

The proposed label application rate of 2000 ppm of Contram ST-1 in the end use MWF equates to a free formaldehyde level of approximately 300 ppm given the product specification of 14 to 16% available formaldehyde. Since formaldehyde has a significant vapor pressure (1 mm Hg at 25 C as formaldehyde in formalin), the vapor inhalation exposure is the primary route of exposure. Inhalation exposure to the vapor is considered to be protective of exposure to the MWF aerosols containing formaldehyde as well as formaldehyde vapors that evaporate from MWF.

## 5.1 Submitted Data

The applicant submitted a machinist exposure study which is discussed below:

*MRID 475558-31, UK Exposure Study, Performed by the Lubrizol Corporation, Completed February 7, 2008*

The purpose of this study was to measure worker exposures to formaldehyde and oil mist during the use of metal working fluids treated with Contran ST-1. This study was conducted at a machining facility in the UK where Contran ST-1 was used in the MWF at a target treatment rate of 1500 ppm as MBM. Two machines (#1, C27 and #2, C133) that used treated MWF and one machine (#3, V38) that used neat oil, that did not contain MBM, were included in the study. Both Machines C27 and C133 were computer numerical controlled (CNC) and they both were used to machine cast steel. The machining operations were milling and drilling at Machine C27 and milling, drilling, threading and trepan cutting at Machine C133. Both machines used low oil semi-synthetic MWF. The levels of MBM in the MWF were measured in samples taken from each machine and ranged from 640 to 860 mg/liter prior to the study and 1470 to 1450 mg/liter during the study.

From the pictures included in the study report, both machines C27 and C133 appear to be semi-enclosed with at least one side being open. The enclosure for Machine C27 appears to be connected via flexible duct to what is probably a mist eliminator while the enclosure for Machine C133 does not appear to be connected to a mist eliminator.

Real time measurements of oil mist were collected using a MIE DataRAM real time aerosol monitor that was calibrated before the study. Real time measurements of formaldehyde and morpholine were also collected using an Innova Model 1412 photoacoustic field gas monitor using appropriate optical filters. Air samples for formaldehyde were collected using glass fiber filters treated with dinitrophenyl hydrazine (DNPH). The flow rate was one liter per minute and the sample durations ranged from 80 to 480 minutes. The samples were analyzed using HSE method 78 which involves desorption of the filters with actonitrile and analysis using HPLC with UV-VIS detection. This method has an LOQ of 0.05 ug/sample which equates to air concentrations of 0.1 to 0.6 $ug/m^3$ (0.08 to 0.5 ppb) depending on the duration of the sample. The real time measurements and area air samples were taken in the vicinity of the machines near the operator positions. Personal samples were also taken on the operators of those same machines. Background area samples were taken near a machine that did not use biocides and in non-machining areas such as the vending area and cafeteria.

The formaldehyde levels measured by the Innova instrument included many values below zero and were considered by the study author to be invalid. EPA agrees with this conclusion and also suspects that the morpholine levels may not been be accurately measured. Therefore the Innova instrument results are not included in this review.

A summary of the formaldehyde air sample results and associated oil mist levels is included in Table 4. In general the formaldehyde levels in the machining areas of were very low and ranged from less than 1 ppb to 6.2 ppb with an average of approximately 2 ppb. The formaldehyde levels in the background areas ranged from less than 1 ppb to 2.8 ppb. The average oil mist levels ranged from 0.137 to 0.296 mg/m$^3$ and the maximum oil mist levels ranged from 0.211 to 0.932 mg/m$^3$. The highest levels occurred at machine C27.

**Table 4 – Summary of Air Sample Results from the Lubrizol Study**

| Sample Type* | Location | Day | Sample Duration (Minutes) | Formaldehyde (ppb) | Average Oil Mist (mg/m$^3$) | Maximum Oil Mist (mg/m$^3$) |
|---|---|---|---|---|---|---|
| GA - Background at Machine V38 where no biocide was used | Operator Position<br>1 meter from machine | 1 | 422<br>438 | 0.81<br>0.90 | NA | NA |
| | Same as for Day 1 | 2 | 318<br>320 | 0.98<br>1.30 | NA | NA |
| | Operator Position | 3 | NA | NA | 0.137 | 0.211 |
| GA - Background Vending Area | | 3 | 80<br>330 | 2.77<br>1.55 | NA | NA |
| GA – Non Machining Area | Near cafeteria 25M from nearest machine | NA | NA | NA | 0.162 | 0.233 |
| GA – Machine C27 | Operator Position<br>1 meter from machine | 1 | 393<br>395 | 1.71<br>1.79 | 0.241<br>0.296 | 0.395<br>0.932 |
| | Same as above | 2 | 476<br>480 | 2.20<br>1.47 | NA | NA |
| | Same as above | 3 | 452<br>453 | 0.90<br>0.98 | 0.173 | 0.379 |
| GA – Machine C133 | Operator Position<br>2 meters from machine | 1 | 227<br>227 | 2.20<br>1.55 | NA | NA |
| | Same as above | 2 | 480<br>480 | 1.63<br>6.19 | 0.149<br>0.172 | 0.231<br>0.243 |
| | Same as above | 3 | 414<br>410 | 3.26<br>1.30 | NA | NA |
| PBZ | Machine C27<br>Machine C133 | 2 | 149<br>138 | 1.71<br>2.20 | NA | NA |
| PBZ | Machine C27<br>Machine C133 | 3 | 312<br>295 | 1.14<br>1.30 | NA | NA |

*GA = general area, PBZ = personal breathing zone

## 5.2 Literature Data

In addition to the study submitted by Lubrizol, there are studies reported in the literature of worker exposures to formaldehyde and oil mist during the use of MWFs. These studies are discussed below.

Formaldehyde Results from the Literature

There are a few studies in the literature which report levels of formaldehyde that is associated with the use of MWF. A listing of these studies is included in Table 5. In the Linnainmaa and Cohen studies, hexahydro-1,3,5 tris (2-hydroxyethyl)-s-triazine (HHT) was used as a biocide and in the remaining studies the biocide used was not reported. In the Lillienberg study the highest levels were recorded in a shop that had recirculating air. In the Suuronen study, the authors reported that ventilation measures and the use of enclosures varied in the workshops and some of the local exhaust equipment was found ineffective; however, they concluded that the overall standard of exposure control was nevertheless found to be reasonable good throughout the companies. Oil mist samples were also collected in ten shops during the Suuronen study and the results ranged from <0.010 to 0.60 mg/m$^3$ with a mean of 0.14 mg/m$^3$. The highest concentrations of oil mist (0.60 mg/m$^3$) were measured during a process with several open-face grinders that did not have local exhaust ventilation. Unfortunately, it is not known if the formaldehyde levels correlated with the mist levels since only summary data are included in the article.

**Table 5 – MWF Formaldehyde Exposures Reported in the Literature**

| Study | Type of Operation Sampled | Biocide Used | Air Sample Type* | Formaldehyde (ug/m$^3$) |
|---|---|---|---|---|
| Godderis, 2007 | Secondary aluminum plant with extrusion presses, hot rolling mills and cold rolling mills | Unknown | GA | 20 to 30 (n=6) |
| Lillienberg, 2008 | 5 machine shops in 3 companies that machined steel, aluminum and iron. Data are listed by company. | Unknown | PBZ | 87 to 154 (n=4)<br>2 to 42 (n=33)<br>1 to 7 (n=16) |
| Suuronen, 2008 | 10 metal machine shops that made tools, bodies and parts for machines and vehicles. Formaldehyde samples were collected in Sep Pak cartridges with a sample duration of 2 hours. | Unknown | PBZ | 11 to 150 (n=42) |
| Linnainmaa, 2003 | Blade grinding (8 shops) General machining (10 Shops) | HHT | PBZ | 8.1 to 179 ppb (n=21) |
| Cohen, 1994 | Steel rolling mills, manufactures of automotive transmissions, industrial machinery, automobiles and aluminum cans | HHT | PBZ | <20 to 490 ppb (n=88) |

*GA = general area, PBZ = personal breathing zone

Oil Mist Results from the Literature

There are several dozen studies of oil mist air exposure reported in the literature; however, most of these studies used filter based air sampling methods. There is a literature study (Obrien, 2001), however, where direct reading instruments were used to measure exposures in 23 small machine shops. These 23 shops were a subset of 79 shops that were being studied by the National Institute of Occupational Safety and Health (Piacitelli, 2001) to assess the range of worker exposures associated with a variety of existing engineering controls. The shops were selected to represent a range of sizes, machining operations, machine age, fluid types and engineering controls. Real time oil mist concentrations were measured using an MIE DataRAM Aerosol Photometer while concurrent air samples were collected using filters in either closed face cassettes or cassettes preceded by thoracic cylones. The air samples were analyzed for both total mass and extractable mass using a NIOSH/ASTM provisional method that is intended to differentiate the MWF specific components of the collected particulate from the non-MWF fraction (such as metals and background particulate). The results of the DataRAM readings and air samples are summarized in Table 6. A comparison of the 8 hour TWA results obtained from the DataRAM with the results of the air sampling indicated that the DataRAM TWAs were approximately 1.5 to 2.0 times greater than the corresponding air sample TWAs depending upon the type of MWF and fraction considered. The authors recommended that correction factors of 0.7 and 0.5 for straight oils and water based fluids, respectively, could be used to adjust the DataRAM readings to estimate results that would be obtained using air samples.

**Table 6 – Machine Shop Oil Mist Exposures**

| | Number of Shops Monitored | Minimum | Average | 95th Percentile | Maximum |
|---|---|---|---|---|---|
| **Short Term DataRAM Readings (mg/m$^3$)** | | | | | |
| Instantaneous Peak | 23 | 0.28 | 5.15 | 17.6 | 21.3 |
| 1 Minute Peak | 23 | 0.14 | 2.13 | 5.94 | 7.97 |
| 15 Minute Peak | 23 | 0.06 | 1.35 | 3.0 | 7.24 |
| **8 Hour TWA DataRAM Readings and Air Sample Results (mg/m$^3$)** | | | | | |
| 8 Hour TWA DataRAM Readings | 23 | 0.04 | 0.55 | 1.25 | 1.82 |
| Closed Face Cassette/Total Mass | 23 | 0.03 | 0.52 | 1.31 | 1.36 |
| Closed Face Cassette/Extractable Mass | 23 | 0.01 | 0.45 | 1.13 | 1.30 |
| Cyclone/Total Mass | 23 | 0.04 | 0.38 | 1.08 | 1.15 |
| Cyclone/Extractable | 23 | 0.01 | 0.32 | 0.96 | 1.11 |

Source: Obrien, 2001

### 5.3 Estimated Exposure to Formaldehyde

The submitted study indicated that formaldehyde levels in the work areas ranged from 1 ppb to 6.2 ppb with an average of approximately 2 ppb while formaldehyde levels in the background areas ranged from less than 1 ppb to 2.8 ppb. The literature data and previously submitted studies suggest that formaldehyde exposures were much higher than those recorded in the Lubrizol study, particularly when HHT was used. Because Contram ST-1 was not used in these studies, it is not known if the difference was due a more rapid release rate of other formaldehyde releasers such as HHT or if the difference was due to other machine shop conditions such a higher work rate or less ventilation. A comparison of the oil mist data from the Lubrizol study vs. the data reported in a literature study (Obrien, 2001) suggests that oil mists levels reported in the Lubrizol study were somewhat lower than the literature data, but the difference was not as great as the difference was for formaldehyde. In the Obrien study, the average 8 hour TWA for oil mist levels was 0.55 mg/m$^3$ while the average oil mist level was 0.2 mg/m$^3$ in the Lubrizol study. It is important to note that the same type of instrument (an MIE DataRAM Aerosol Photometer) was used in both the Lubrizol and the Obrien studies.

The submitted data in conjunction with the data available from the literature appears to suggest that formaldehyde exposures from the use of Lubrizol will be lower than the formaldehyde exposures recorded during the use of HHT and will not exceed the EPA level of concern of 100 ppb. However, this preliminary conclusion is based on the assumption that the Lubrizol study was conducted under typical machine shop conditions. It is recommended that additional formaldehyde samples be collected in a several additional machine shops to verify the extremely low levels of exposure measured during the Lubrizol study. These samples should be collected using sampling times of 10-15 minutes each so that results will be comparable to the LOC of 100 ppb which is a peak value.

If additional sampling indicates that formaldehyde exposures exceed the LOC under typical machine shop conditions, then engineering controls such as machine enclosures and local exhaust ventilation will be required. It will also be necessary to collect additional samples to verify the performance of the machine enclosures, because such systems were often designed for the control of oil mist and were not intended to control formaldehyde vapors. This is particularly true for machine enclosures connected to mist elimination systems where the air is recirculated back into the work area after passing through a filtration unit. While such systems can be effective for trapping aerosols that consist of oil mist and typical biocides that are essentially non-volatile, these systems are not effective for volatile biocides such as formaldehyde unless they are vented to the outside.

## 6.0 Human Studies Considerations

All of the exposure studies mentioned in this risk assessment (Cohen, 1994, Godderis, 2008, Lillienberg, 2008, Linnainmaa, 2003, Obrien, 2001, Piacitelli, 2001, and Suuronen, 2008) have been determined by the OPP ethics reviewers to be observational in nature and did not involve intentional exposure to human subjects.

## 7.0 References:

Cohen, 1994. A Study of Formaldehyde Exposures from Metalworking Fluid Operations Using Hexahydro-1,3,5-Tris (2-Hydroxyethyl)-S- Triazine. MRID 473354-02, H. J. Cohen, University of New Haven, May 3, 1994

Conolly, 2004. Human Respiratory Tract Cancer Risks of Inhaled Formaldehyde: Dose-Response Predictions Derived From Biologically-Motivated Computational Modeling of a Combined Rodent and Human Dataset. Conolly, R. B., Kimbell, J.S., Janszen, D., Scholsser, P. M., Kalisak, D., Preston, J., and Miller, F.J., Toxicological Sciences: 82 (279-296).

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Lillienberg, 2008. Exposure to Metal Working Fluid Aerosols and Determinants of Exposure. Lillienburg, L., Burdorf, A., Mathiasson, L., Thorneby, L., Annuals Occupational Hygiene, Volume 52, Number 7, pp 597-605.

Linnainmaa, 2003. Control of Worker's Exposure to Airborne Endotoxins During Use of Metalworking Fluids. Markuu Linnainmaa, Hannu Kivirata, Juha Laitinen and Sirpa Laitinen, Kuopio Regional Institute of Occupational Health and National Public Health Institute Department of Environmental Health, Kupio, Finland, AIHA Journal 64:496-5000, July/August 2003.

Obrien, 2001. An Evaluation of Short-Term Exposures to Metalworking Fluids in Small Machine Shops. Obrien, D.M., Piacitelli, G. M., Sieber, W. K., Hughes, R.T., Catalano, J.D., American Industrial Hygiene Association Journal, Volume 62, pp 342-348.

Piacitelli, 2001. Metal Working Fluid Exposures in Small Machine Shops: An Overview. Piacitelli, G. M., Sieber, Obrien, D.M., W. K., Hughes, R.T., Catalano, J.D., American Industrial Hygiene Association Journal, Volume 62, pp 356-370.

Suuronen, 2008. Respiratory Exposure to Components of Water-Miscible Metalworking Fluids. Suuronen, K., Henriks-Eckerman, M-L, Riala, R., Tuomi, T., Annuals Occupational Hygiene, Volume 52, Number 7, pp 604-614.