Trimellitic Anhydride (i.e. TMA) March 19, 2012

I. **Identification**

Chemical Name: Trimellitic Anhydride
Synonyms: Anhydrotrimellitic acid; 1,2,4-benzenetricarboxylic anhydride
CAS Number: 552-30-7
Molecular Formula: $C_9H_4O_5$

II. **Chemical and Physical Properties**

Physical State: off-white flakes, needles, or crystals
Molecular Weight: 192.12 gm/mole
Conversion Factors: 1 ppm = 7.86 mg/m3 and 1 mg/m3 = 0.13 ppm
Melting Point: 161 to 165 °C
Boiling Point: 240 to 245 °C
Vapor Pressure: 1.2 X 10-7 mmHg at 25 °C
Odor Description and Threshold: odorless
Flash Point: 227 °C (open cup)
Specific Gravity: 1.54 gm/ml at 20 C
Solubility in Water: complete
Stability: TMA undergoes rapid hydrolysis to trimellitic acid when subject to aqueous conditions

III. **Uses and Volume**

TMA is used in the synthesis of, or curing agent for, various plastic, alkyl and epoxy resins, plasticizers, polyimide resin paints, water soluble alkyd resins, dipping agents, coatings, wall and floor coverings, and insulation enamels for cable and wire. World-wide production has been reported at 110,250 tons.

IV. **Toxicology Data**

A. Acute Toxicity and Irritancy

1. Oral

No studies identified and reviewed.

2. Eye

No studies identified and reviewed.

3. Skin

a. Irritation

No studies identified and reviewed.

b. Sensitization

Farraj et al 2006 studied whether to route of sensitization exposure would influence pathologic and immunologic effects after intranasal challenge to TMA. Mice were dosed with TMA in ethyl acetate/olive oil on the ear or by intranasal instillation. Doses were applied on day 1 and 3, challenged on day 17 and 27, and then mice killed 48 hours later. The different doses/challenges/routes were varied such that the study included six different test groups with differing dose routes. Histopathology was done on the exposed ears to find contact hypersensitivity in the skin. All routes of sensitization dose and challenge caused increased serum IgE.

TLV references other animal studies (Zhang et al 2002, Pauluhn et al 2002) indicating dermal contact may cause or exacerbate respiratory sensitization.

c. Absorption

TLV documentation 2008 references Zhang et al 2002 for evidence of dermal absorption leading to possible respiratory sensitization. While no skin irritation was observed after dosed with TMA powder, dose-dependent TMA antibodies were measured. Also referenced was Pauluhn et al 2002 who mixed TMA with acetone and olive oil and founds the same effects observed for inhalation-only exposed rats.

4. Inhalation

TLV 2008 Document stated Arts et al 2001 found rat NOEL for changes in breathing patterns of 14 mg/M3 in two strains (MMAD 0.5 and 2.2 um).

B. Genotoxicity

Negative in all tests reported in TLV doc 2008.

C. Metabolism and Pharmacokinetics

No studies identified and reviewed.

D. Developmental / Reproductive Toxicity

TLV 2008 Document states Ryan et al 1989 found Rats and Guinea pig neonates did not show TMA effects including antibodies seen in dams.

E. Subacute

Leach et al 1987 dosed SD rats via inhalation to 0, 0.01, 0.03, or 0.3 mg/M3 1 um MMDA TMA for 6 hr/day for varying durations. Two groups were given either five or ten days dosages with no follow-up challenge. Two groups of dosed rats were given a single follow-up dose post-exposure; one group after 12 days, another after 12 weeks. No effects were observed after 5 exposures. After ten exposures the following increased with a dose-response effect: absolute and relative lung weights, external hemorrhagic lung foci, alveolar macrophage accumulation, alveolar hemorrhage, pneumonitis, and lung and mediastinal lymph node non-specific IgG and complement (C3). Rats examined 12 days post exposure did not have these effects nor did the rats dosed once 12 weeks post-exposure. Rats dosed once 12 days post-exposure showed the same effects as at the end of the 12-day dosage. The lowest dose where a statistically significant effect was observed in 0.03 mg/M3 dose group (actual mean exposure measured was 0.037 mg/M3), and the next lowest dose (the NOAEL) was 0.01 mg/M3. The LOAEL was found in the ten-day dosage rats' mean alveolar macrophage accumulation and mean alveolar hemorrhage values. At this 0.03 mg/M3 dose, both these effects severity scored '1' on a scale from 0 to 4. The external hemorrhagic lung foci were elevated in the 0.3 mg/M3 dose 10-day dose-only group and in the 0.1 and 0.3 mg/M3 10-day/rest 12 re-challenge dose group. One interesting note by the authors: all other tissues and organs were unaffected by the exposure, only the lungs were affected despite the serum antibodies high. The antigen-antibody reaction and subsequent destructive mechanisms were local (to the lung) and not systemic. The immunopathology showed antibody was being produced by mediastinal lymph nodes that drain the lungs and not by bronchus-associated lymphoid tissue.

F. Subchronic Toxicity

Zeiss et al 1989 did a three-part investigation of the effects of short-term intermittent doses occurring with several days of no exposure between doses. Part 1: Six SD rats inhaled 0.5 mg/M3 powder for 6 hrs on days 1, 5, and 10. Then on day 29 rats were exposed to a 6-hr 0.54 mg/M3 challenge dose then killed 18 hours later and examined. Antibody levels rose from day 5 to 20, and IgA antibodies correlated with and increase in hemorrhagic lung foci. Part 2: 18 SD rats inhaled 0.33 mg/M3 powder for 6 hrs on days 1, 5, and 10. Then on day 22, only 12 of the 18 rats were exposed to a 6-hr 0.3 mg/M3 challenge dose then killed 18 hours later and examined. Rats not challenged showed markedly reduced lung foci, weight, and volume compared to challenged rats. Part 3: Eight SD rats inhaled 0.5 mg/M3 powder for 6 hrs on days 1 and 5. Then on day 29 were exposed to a 6-hr 0.5 mg/M3 challenge dose then killed 18 hours later and examined. Significant numbers of hemorrhagic lung foci and increases in relative lung weight were found, and good correlation was found between lung injury and antibody levels. Overall results indicate short-term intermittent exposure can cause sensitization in rats, and re-exposure can cause lung injury correlated with antibody levels.

Zhang et al 2006 dosed rats at 0.04, 0.4, 4 or 40 mg/M3 TMA for ten minutes, once a week for over ten weeks. Semiquantitative pathology on the lungs included: 1) eosinophilic granulomatous interstitial pneumonia, 2) perivascular eosinophilis, 3) hyperplasia of bronchus-associated lymphoid tissue, and 4) peribronchiolar plasma cell infiltrates. The scores, based on both severity and distribution, in the lowest exposure group (0.04 mg/M3) showed perivascular eosinophilis and hyperplasia of bronchus-associated lymphoid tissue. In general, there were increases in all four scores as the dose increased.

G. Chronic Toxicity and Carcinogenicity

Leach et al 1989 conducted a six-part study using SD rats dosed via inhalation to 0, 0.002, 0.015 or 0.05 mg/M3 respirable size (approx 2 um MMAD) TMA for 6 hr/day, 5 days/week for 13 weeks. Part 1: evaluated TMA-specific antibody appearance/disappearance time: rats were bled weekly during the 13 week dosage and bi-weekly thereafter – TMA-specific serum antibody levels were measured for 45 weeks. Found serum levels spiked at week 6, but generally was lower until weeks 13 to 22, then declined thereafter. Part 2: evaluated time course of TMA toxicity development and tolerance: 14 rats dosed with 0.05 mg/M3 were killed in pairs at weeks 1, 2, 3, 4, 6, 8 and 10 – lungs were examined and external hemorrhagic focal lesions counted. External lung foci was about 10 week one, peaked at week two (approx 340), declined about 25% each for weeks 3, 4, 6. Part 3: evaluated effects after 6.5 weeks of exposure: 40 male rats exposed to 0, 0.002, 0.015 or 0.05 mg/M3 were killed after 32 exposures and all major tissues weighed, lungs examined microscopically, hematology parameters and TMA-specific antibodies determined. Mean number of external hemorrhagic lung foci in male rats was statistically significant at 0.05 mg/M3 (LOAEL) but not at 0.015 mg/M3 (NOAEL) at 6.5 and 13 week exposures but not in post-exposure/challenge groups. Female rats in 0.050 mg/M3 (NOAEL) group had no lung foci. Part 4: evaluated effects in male vs female after 13 weeks exposure: 80 rats (10/sex/dosage) killed after 13 weeks and all major tissues weighed, lungs examined microscopically, hematology parameters and TMA-specific antibodies determined. Male rats exposed to 0.05 mg/M3 exhibited a significant increase in lung foci compared to controls. Female rats exposed to 0.015 and 0.05 mg/M3 shows slight increase in lung foci but at about the same frequency as the 0.002 mg/M3 male rat group and at only ten times less than the 0.05 mg/M3 dosed male rats, i.e. there was a noticeable difference between male and female rat. Male rats

showed about twice the female rat serum antibody levels, and both were significantly leveled compared to controls. Part 5: evaluated effects of re-exposure after brief rest: 48 male rats (12/dosage) exposed for 13 weeks were held exposure-free 3 weeks, half (6 rats/dosage) were challenged with single 0.05 mg/M3 6-hr dose, other half were not exposed, and all major tissues weighed, lungs examined microscopically, hematology parameters and TMA-specific antibodies determined. Lung foci returns to near-normal levels in both challenged and unchallenged groups. Lung weight and volume increased in both groups in dose-response manner with them slightly higher in challenge group. Part 6: evaluated long-term recovery potential from earlier adverse effects and effects of re-exposure after serum antibody levels had declined: 12 males from 0.05 mg/M3 and 6 from each of the other dosage groups exposed for 13 weeks were held for 38 weeks without post-exposure, 6 rats in 0.050 mg/M3 group were challenged with single 0.05 mg/M3 6-hr dose, other 6 were unchallenged, and all major tissues weighed, lungs examined microscopically, hematology parameters and TMA-specific antibodies determined. No effects found except the challenge group showed an increased lung weight but not volume. Serum antibody levels were still increased over controls.

None of the references cited herein mentioned possible carcinogenicity, nor did any literature searches find abstracts mentioning carcinogenicity for TMA, and the TLV 2008 Document stated no studies were found on carcinogenicity.

H. Clinical Studies

Patterson et al 1978 studied antihapten antibody production in humans. Findings included IgE antibody appears correlated with the rhinitis-asthma syndrome in 3 of 5 workers; serum IgG antibody activity was elevated in workers with asthma, LRSS or both compared with asymptomatic workers; IgA antibody activity was elevated in workers with respiratory syndromes except two; and IgM antibody activity was highest in four symptomatic workers but was not clearly associated with disease.

V. **Human Use And Experience**

Letz et al 1987 performed a cross-sectional study of nine workers in a drum manufacturing plant using TMA powder. Workers were evaluated with questionnaires, physical examination screening pulmonary function tests, serial peak expiratory flow rate and serum antibody levels. Airborne TMA levels were measured as high as 4 mg/M3. Four workers had irritant symptoms; three had IgG levels indicating late respiratory systemic syndrome of which two had peak expiratory flow rate drops (>20%) after exposure.

Barker et al 1998 studied 506 workers in several workplaces with exposure to acid anhydrides. Workplace air sampling allowed exposure categorization. Signs/symptom surveys were completed, as well as skin prick tests. Only in the factory handling TMA workers had increased prevalence of sensitization and work-related respiratory symptoms with increasing full shift exposure. Workers showed increasing risk of an immediate skin prick test reaction to acid anhydride human serum albumin conjugate. Two, equal number cohorts based upon full shift exposures: 0.001 to 0.0114 mg/M3 – OR 11.07 (0.55 – 222.73) and >0.0114 mg/M3 – OR 16.22 (0.86 – 304.56).

Grammer et al 1999 studied 286 workers in a TMA manufacturing facility for immunologically mediated respiratory disease. Workers were divided into five exposure groups and examined for disease development for three consecutive years. Workers were placed in exposure groups by a Hygienist (blinded to disease outcome) based upon Hygiene sampling and historic knowledge. Workers completed annual symptom survey form, demographic clinical information, spirometry and chest radiography, blood tests for immunoglobulin G and E antibodies. Workers with positive sign of antibodies were given interview, examination, and skin-test by a physician. Prevalence of disease tended to increase with exposure. Mean full-shift personal air sampling was performed, and the Hygienist categorized the workers' exposure into five groups. The exposure level in mg/M3 for groups and disease prevalence was: 0.13 (29%), 0.036 (4%), 0.002 (5%), 0.00051 (0%) and <0.00053 (0%). The workers with exposure less than 0.002 mg/M3 did not develop disease. To quote part of the conclusion:

Exposure Class	Range (mg/m^3)	Mean (mg/m^3)
1	0.0029–1.7	0.13
2	0.0023–1.9	0.036
3	0.0001–0.12	0.002
4	0.00023–0.0024	0.00051
5	<0.00045–<0.00060	<0.00053

"The relationship between exposure level, sensitization, and development of occupational immunologic lung disease has important implications. First, the decreasing proportion of employees with positive serology or disease with exposure class is consistent with other reported studies of occupational sensitizers, of both high and low molecular weight. This study also demonstrated a threshold in that exposure levels in classes 4 and 5 did not result in disease in any of 122 employees. Second, because individuals in exposure classes 4 or 5 had little risk of sensitization or disease, it would

Exposure Class	Total Employees	No. With IgG Antibody		With IgE Antibody		With IgG Disease		With IgE Disease	
		n	%	*n*	%	*n*	%	*n*	%
1	28	12	43	7	25	3	11	5	18
2	57	13	23	6	11	1	2	1	2
3	79	10	13	5	6	3	4	1	1
4	98	9	9	0	0	0	0	0	0
5	24	0	0	0	0	0	0	0	0

seem that individuals exposed to less than 0.0005 mg/m3 (as these individuals were) probably would not need additional efforts at exposure reduction, nor would they need to routinely participate in surveillance studies. Finally, efforts at exposure reduction such as improved ventilation or process enclosure would best be directed toward individuals in the higher exposure classes."

To follow-up, Grammer et al 2000 studied 42 TMA-induced immunologic lung disease cases after transfer into low or no exposure work (class 4 or 5 in Grammer et al 1999). After at least one year 36 workers were asymptomatic with normal spirometry. The other six showed only mild intermittent symptoms or mild abnormalities on spirometry. About half of the workers showed a decline in antibody titer.

Barker et al 2000 performed a retrospective cohort study of 506 workers some of whom were exposed to TMA. Study included skin-prick tests to conjugates of TMA, histories of smoking and employment, pulmonary function testing, and exposure monitoring and assessments. An association was found between sensitization and bronchial hyperresponsiveness. However there was no relationship between cumulative exposure and BHR.

Zeiss et al 2002 studied 474 chemical manufacturing workers with a one-year cross-sectional evaluation of serologic and clinical outcomes. A Hygienist blindly assigned employees to one of five exposure classes defined by geometric mean (mg/M3) TMA: 0.17 (25 employees), 0.087 (70), and the three other groups had no detectable TMA with LoQ as: <0.00055 (148), <0.00041 (172) and <0.00053 (43). Newly hired employees' syndromes and antibodies were compared to previous employees'. This group had higher prevalence of asthma/rhinitis, late respiratory systemic syndrome, late asthma, irritant, total immunologic (antibodies). Of the previous employees, positive findings were distributed across all exposure groups "*because those employees who had developed an immunologic syndrome were intentionally moved to lower exposure jobs over the years…*". New employee group demographics were evaluated, and smoking, current or former, was the only variable associated with total TMA antibody levels.

Blomqvist et al 2005 investigated powder painting facilities with possible use of TMA along with other acid anhydrides. IgG but not IgE antibodies against TMA were detected in some workers. However, IgG antibodies were detected in the unexposed/control group. Some people in the unexposed/control group were sensitized. Some symptoms were related to dose. Level of TMA antibodies was not related to the exposure level.

VI. **Summary**

TMA exposures and effects have been investigated in workplace studies. Animal trials seem to indicate similar effects as seen in humans in workplaces. TMA primarily causes acute effects to the respiratory tract. Sensitization has been seen with exposure via inhalation and dermal absorption. To avoid allergic reactions, short duration exposures should be controlled. Most workplace investigations involved full shift airborne measurements. The most relevant information was a workplace study by Grammer et al 1999 identifying a human LOAEL of 0.002 and a NOAEL of 0.0005 mg/M3.

VII. **Recommended PEL**

A revised PEL (8-hour) TWA of 0.0005 mg/M3 is recommended for consideration by the HEAC. Also a 15-minute STEL of.002 mg/M3 is recommended for discussion to replace the existing PEL Ceiling limit of 0.04 mg/M3 based upon comments by researchers that antibody production could occur following brief exposures. Exposures controlled to below these concentrations should prevent immunologically-mediated respiratory disease. The primary reference for this PEL recommendation is the workplace study of Grammer et al 1999, which is also a central reference in the ACGIH TLV Documentation.

Other Information:

- OSHA air sampling method 98 (November 1992) specifically for trimellitic anhydride, indicates a reliable quantitation limit (ROQ) of 0.623 ug/M3 (0.229 ug/sample) in a 480 liter air sample collected on a coated glass fiber filter at 2 liters per minute, using high performance liquid chromatography (HPLC) for the analysis. The overall detection limit of the method is indicated to be 0.106 ug/sample.
- NIOSH sampling method 5036 has working range 0.048 to 0.24 mg/M3 for a 400 L sample. The recommended flow rate is 1.5 to 2 liters per minute. Also, the estimated limit of detection is 2 ug. If an air sample was collected at 2 liters per minute for 480 minutes, the estimated limit of detection is approximately 0.002 mg/M3.
- ACGIH TLV (2008): TWA 0.0005 mg/M3, STEL 0.002 mg/M3 inhalable fraction and vapor with Sensitization (SEN) and Skin notations.

VIII. **References**

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