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American Chemistry Council

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VICE PRESIDENT
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January 12, 2005

Wardnei G Penberthy
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N W (7405M)
Washington, D C. 20460

Re: Supplemental Information fot Methyl Ethyl Ketone (MEK) under EPA's Voluntary Children's Chemical Evaluation Program (VCCEP)

Dear Mr Penberthy:

This letter is submitted on behalf of the American Chemistry Council Ketones Panel VCCEP Task Group and includes the enclosed information addressing the following items:

1. Exposure Considerations foi Prospective Parents;
2. Daily Exposure Aggregates; and
3 TLV Use to Calculate Exposure to Nursing Infants

With regard to exposure considerations for prospective parents, portions of this supplemental analysis were not presented in the original VCCEP submission but were presented at the TERA peer consultation meeting on February 19, 2004.

If you have any questions concerning this letter, please contact William Gulledge, Manager of the Ketones Panel, at (703) 741-5613 or at William_Gulledge@americanchemistry com

Sincerely yours,

Enclosure

cc: Jennifer G. Seed, EPA
Dan Briggs, TERA

Supplemental Information for Methyl Ketone (MEK) Under EPA's Voluntary Children's Chemical Evaluation Program (VCCEP)

Exposure Considerations for Prospective Parents:

Supplemental analyses were shared at the TERA peer consultation meeting (February 19, 2004) to address potential exposures of prospective parents from anthropogenic MEK sources. The exposure estimates presented in the MEK VCCEP submission for 16-19 year olds are considered reasonable estimates for adults, based upon similar exposure factors (i.e., body weight, inhalation rates, usage patterns and contact times:

- *Body Weights and Inhalation Rates*: The USEPA exposure factors handbook provides the information set below, indicating that given the same air concentration, inhalation exposures calculated for 16-19 years olds will be higher than for adults based upon a greater inhalation rate/body weight ratio for teens. For this screening assessment, teen exposures were used as representative of adults without adjustment. The IR/BW ratios indicate adult female exposures would be ~25% lower than teens, and adult males ~10% lower than teens.

Age	BW (kg)	Inhalation Rate (m^3/day)	IR/BW (m^3/kg-day)
16-19 yr	67.1	14.2	0.21
Adult F	65.4	11.3	0.17
Adult M	78.1	15.2	0.19
Adult M&F*	71.8	13.2	0.18

*Average of M and F

- *Usage Patterns and Contact Times*: The older teen category contact and/or usage of MEK products were based upon adult usage patterns and direct product use. Thus, the exposures calculated for older teens can also be used to represent adults.

In addition to the exposure pathways presented in the submission, occupational exposures may also occur for adults. While the TLV is 200 ppm (590 mg/m^3), VCCEP sponsors are not aware of any occupational situation where the TLV is constantly maintained. Rather, after conducting a literature search, the sponsors found the highest 8 hr TWA for a US or location not specified occupational setting was 45 ppm (~135 mg/m^3), in a study of male workers. Most occupational MEK exposures, even for shorter periods, were $\leq$ 10 ppm.

Conclusions for chronic exposures presented for children apply equally to adults:

- *Background Exposures*: Exposures from ambient air, indoor air, water, and soil are all very low compared to the IRIS RfC of 5.0 mg/m^3 and the RfD of 0.6 mg/kg/day.

- *Facility Releases*: EPA has determined that facility releases may not reasonably be anticipated to result in adverse health effects, with conservative estimation methods resulting in maximum concentrations well below the RfC.
- *Natural Exposures*: Exposures from food were not calculated separately for adults. MEK naturally occurs in many food items across all food categories, especially in cheese and yogurt. However, because analysis and quantified levels are not available for all food items, potential exposures via this pathway were estimated as a range based upon average food intake and maximum and minimum values of MEK for food items. Given the common occurrence of MEK in food but limited quantitative data, this screening level analysis was considered the most appropriate for estimating the relative contribution of this pathway. If maximum food intake values were used, this pathway would represent a greater portion of overall exposure. Since the goal of the submission was to determine safety of anthropogenic MEK exposures, the average food intake value was used so that the relative contribution of anthropogenic sources would not be underestimated. Food intake was also compared to a chronic benchmark (RfD), further supporting the use of an average value. While adult food exposures were not estimated, the variation between adult and teen exposures is unlikely to be greater than that for the range of exposures within each category. For teens, ingestion of MEK via natural presence in food was estimated to be 0.0003 – 0.14 mg/kg/day for a one-day exposure, and 0.0002 – 0.1 mg/kg/day for an annual average daily exposure.
- *Consumer Product Exposures*: As indicated above, exposure estimates for consumer product use for the teen category can be used as estimates of adult exposure, and indicate exposure levels well below the RfC and RfD.

Conclusions for acute exposures from consumer product use also apply to adults. A supplemental table in which the acute exposure estimates included in the VCCEP submission were expressed in several alternate time frames was distributed at the peer consultation meeting (Table 1). The information in this table can be compared to the following alternate acute benchmarks.

For acute exposures, an alternate 24-hour exposure benchmark was calculated based upon the RfC, but removing the 10-fold uncertainty factor:

Adjusted RfC = 50 mg/m^3/day

For day of use consumer product exposure scenarios, all 24 hr TWAs were < 17 mg/m^3/day.

For a shorter TWA, in addition to the 10-fold uncertainty factor the benchmark is also adjusted to 7 hr/24 hr as animal exposures were for 7 hr /day. This results in an adjusted acute RfC of 50 mg/m^3 X (24/7) = 171 mg/m^3. In comparison, all 4 hour TWAs for consumer product use scenarios were < 100 mg/m^3 (or, if adjusted to a 7 hour period, < 57 mg/m^3).

The highest occupational 8-hour TWA reported in the literature was 135 mg/m^3, which is lower than the adjusted acute RfC of 171 mg/m^3.

Thus, compared to the RfC adjusted for a shorter time period, exposures are all below the adjusted RfC.

MEK was not considered a developmental or reproductive toxicant because the toxic endpoint was lower offspring body weight at concentrations that were high enough to cause maternal toxicity. This effect was not associated with a specific developmental stage, and thus likely happened over time rather than during a sensitive window of exposure.

Daily exposure aggregates:

Background exposures (air, water, and soil) were negligible based upon monitoring data (typically below detection) and physical chemical properties. Highest reported air concentrations were for 0.04 mg/m^3 for indoor air and 0.002 mg/m^3 annual average for a non-residential area. Even assuming constant exposure to 0.04 mg/m^3, using age-specific inhalation rates and body weights and an inhalation fraction of 0.5, estimated exposures would be <0.015 mg/kg/day.

The main exposure pathways for MEK are natural occurrence in food and potential consumer product use. Results are presented in Tables 2-3 on a daily basis and Tables 4-5 on a chronic annual basis. The estimated doses on a chronic annual basis can be compared to the RfD of 0.6 mg/kg/day. For acute exposures (daily basis), an alternate 24-hour exposure benchmark can be calculated based upon the RfD, but removing the 10-fold subchronic:chronic uncertainty factor:

Adjusted RfD = 6 mg/kg/day

On a daily basis, it is unlikely that a person would be exposed to all consumer products on a given day. Thus, for aggregation of all consumer products, a chronic basis is more appropriate. It is also unlikely that product use would occur under maximum exposure conditions each time during the year; therefore, aggregation of maximum uses is not considered appropriate. However, it is included here for completeness.

Additional Information on how the TLV was used to calculate exposure to nursing infants:

The estimate of nursing infant exposure from breast milk of occupationally exposed mothers was taken from Fisher et al., 1997. The estimate provided in Fisher was based upon exposure to a maintained TLV. In the VCCEP submission, this estimate was divided by a factor of the TLV/ highest reported 8 hour TWA for a US or location non-specified occupational setting) = 200 ppm / 45 ppm or ~4.

More detail on the analysis of Fisher et al. 1997:
Fisher developed and applied a physiologically based pharmacokinetic lactation model. Model input included:

- Experimentally measured human milk/air and blood/air partition coefficients, which were then divided to give a milk/blood partition coefficient.
- Calculated tissue/blood partition coefficients based upon published tissue/air partition coefficients.
- Metabolic rate constants and physiological parameters derived from the literature.
- An exposure simulation in which the mother was exposed to a constant vapor concentration equal to the TLV throughout the workday, with the exception of work-break periods. The workday was from 8 AM – 5 PM, with breaks taken from 10- 10:30 AM, 12-1 PM, and 3-3:30 PM.
- Infant feeding occurred at work during each break period. The schedule for infant feeding was approximately: 7 AM, 10 AM, Noon, 3 PM, 6 PM, 9 PM, 2 AM and 5 AM. At work, each nursing period started 6 minutes after the occupational exposure stopped.
- The authors indicated that a conservative nursing schedule of 8 feedings of 12 minutes and 115 ml milk each was used (total of 920 ml/day). The authors indicate that on average, lactating women produce 680-840 ml milk/day and average 7-8 feedings/day.
- The PBPK model used represented an improvement over earlier models, as it used a 5 compartment human PBPK lactation model that included a milk compartment that changes volume in response to milk production and suckling. Another improvement was the use of measured milk and blood partition coefficients.
- The PBPK model resulted in an estimated exposure of 12.08 mg MEK/day during occupational exposure to the TLV of 200 ppm.

In the VCCEP submission, the model prediction was then adjusted to a mg/kg/day value using the following values:

- Assumed mother returned to work full time when the child was 2 months of age.
- Average body weight of a 2-12 month old = 7.8 kg based upon USEPA Child Specific Exposure Factors Handbook.
- Adjusted to a mean ingestion rate of 688 ml/day by factor of 688/920 ml, to keep body weight and intake on consistent basis.
- Exposures assumed 5 days/week for 40 weeks.
- All of these assumptions resulted in an annual average daily dose of 0.63 mg/kg/day.

As described in the VCCEP submission, this value is believed to be a bounding estimate of exposure[1] unlikely to occur Many workplaces have a protective reassignment program for pregnant or nursing women to minimize potential exposures. In addition, even without protective reassignment, continuous workplace exposure to the TLV is not expected to occur. Occupational exposure levels reported for US workplaces (ATSDR, 1992; HSDB 2001) were all well below the TLV; most values presented in these reviews were $\leq$ 10 ppm (the highest 8 hour TWA occupational exposure for US or location not specified was 45 ppm for a study of male workers).

Given this information, the sponsors assumed a constant, continuous exposure to the highest reported short-term 8-hour occupational level, and also assumed a direct linear correspondence between exposure and breast milk concentration. The partitioning of MEK, quick absorption via inhalation, and rapid metabolism, support this as a reasonable assumption.

Thus, a more realistic upper bound is believed to be the Fisher modeled divided by a factor of 4 (estimated as the TLV divided by the highest reported 8 hr TWA, or 200 / 45 ~ 4), or 0.16 mg/kg/day. Given the conservative assumptions of the Fisher model, it is felt that this represents a conservative upper estimate of infant exposure. As stated in the report, MEK in pump-collected milk would be likely to volatilize during warming, and if the infant was not at work and was fed only upon returning home (no pumping), the MEK exposure level would be likely to be lower since the number of direct feedings also would be reduced.

[1] Bounding Estimate as defined in USEPA Guidelines for Exposure Assessment, FRL-4129-5: An estimate of exposure, dose or risk that is higher than that incurred by the person in the population with the highest exposure, dose or risk. Bounding estimates are useful in developing statements that exposures, doses, or risks are "not greater than" the estimated value.

Table 1. MEK VCCEP EXPOSURE ASSESSMENT SUPPLEMENTAL TABLE (presented at peer consultation meeting:							
Estimated MEK Air Concentrations for the Exposure Event, Active Use Scenarios							
Scenario	Model	4 hr TWA	24 hr TWA	Estimates for Total Time in Room of Use (Use + After)		Estimates for Time of Active Use	
				Duration	Est. TWA	Duration	Est. TWA
		mg/m^3	mg/m^3	hr	mg/m^3	hr	mg/m^3
Carburetor Cleaner	E-FAST	3.9	0.7	1.00	16	0.37	43
Spray Paint	E-FAST	56	9.3	1.00	224	1.00	224
Wood Stain	E-FAST	92	15.3	2.00	184	1.92	192
Paint Thinner	E-FAST	1.9	0.3	3.00	3	2.75	3
Brush Cleaning	PROMISE	13.7	2.3	0.17	328	0.17	328
Adhesives - Hobby	E-FAST	0.43	0.1	1.00	2	0.50	3
Adhesives - Adult	E-FAST	3.2	0.5	2.00	6	1.40	9
Hobby Model Paint	E-FAST	0.4	0.1	2.00	1	2.00	1

Table 2. **DAILY BASIS: Exposures in mg/kg/day by age group**

	PASSIVE FOR < 16 AGES, ACTIVE FOR 16-19 EXCEPT HOBBY SCENARIOS - AGES 12-15 ALSO ACTIVE					
TYPICAL EXPOSURES	**<1**	**1-2**	**3-5**	**6-11**	**12-15**	**16-19**
FOOD - NATURAL	0.0009 - 0.36	0.0008 - 0.61	0.0007 - 0.39	0.0005 - 0.24	0.0003 - 0.14	0.0003 - 0.14
BREAST MILK BACKGROUND	0.0007 - 0.001					
SUM FOOD*	0.36	0.61	0.39	0.24	0.14	0.14
CARB CLEANER - INHALATION	0.017	0.015	0.013	0.011	0.007	0.018
SPRAY PAINT - INHALATION	0.49	0.44	0.38	0.3	0.19	0.47
WOOD STAIN - INHALATION	0.98	0.87	0.76	0.6	0.38	1
PAINT THINNER LIQUID INHALATION	0.002	0.002	0.001	0.001	0.001	0.002
max PAINT THINNER CLEAN UP INHALATION	0.038	0.035	0.03	0.024	0.015	0.24
max PAINT THINNER DERMAL						0.04
HOBBY ADHESIVE INHALATION	0.003	0.002	0.002	0.002	0.003	0.003
MaxHOBBY ADHESIVE DERMAL						0.0005
ADULT ADHESIVE USE	0.004	0.003	0.003	0.002	0.001	0.003
HOBBY MODEL PAINT INHALATION	0.004	0.004	0.003	0.002	0.004	0.004
sum direct product use	1.538	1.371	1.192	0.942	0.601	1.7805
PRODUCT + FOOD	1.898	1.981	1.582	1.182	0.741	1.9205

*For infants, the higher of breast milk or food was used

Table 3.

DAILY BASIS: Exposures in mg/kg/day by age group

	PASSIVE FOR < 16 AGES, ACTIVE FOR 16-19 EXCEPT HOBBY SCENARIOS - AGES 12-15 ALSO ACTIVE					
MAXIMUM EXPOSURES	<1	1-2	3-5	6-11	12-15	16-19
averageFOOD - NATURAL	0.0009 - 0.36	0.0008 - 0.61	0.0007 - 0.39	0.0005 - 0.24	0.0003 - 0.14	0.0003 - 0.14
BREAST MILK OCCUPATIONALLY EXPOSED MOTHER	0.292					
SUM FOOD*	0.36	0.61	0.39	0.24	0.14	0.14
CARB CLEANER - INHALATION	0.07	0.06	0.05	0.04	0.03	0.07
SPRAY PAINT - INHALATION	1.04	0.93	0.81	0.64	0.41	0.35
WOOD STAIN - INHALATION	1.59	1.42	1.23	0.98	0.62	1.62
PAINT THINNER LIQUID INHALATION	0.03	0.03	0.02	0.02	0.01	0.03
PAINT THINNER CLEAN UP INHALATION	0.038	0.035	0.03	0.024	0.015	0.24
PAINT THINNER DERMAL						0.04
HOBBY ADHESIVE INHALATION	0.008	0.007	0.006	0.005	0.009	0.008
HOBBY ADHESIVE DERMAL						0.0005
ADULT ADHESIVE USE	0.05	0.05	0.04	0.03	0.02	0.06
HOBBY MODEL PAINT INHALATION	0.007	0.007	0.006	0.005	0.008	0.007

*For infants, the higher of breast milk or food was used

Table 4.	ANNUAL BASIS – Exposures in mg/kg/day by age group					
	PASSIVE FOR < 16 AGES, ACTIVE FOR 16-19 EXCEPT HOBBY SCENARIOS - AGES 12-15 ALSO ACTIVE					
	<1	1-2	3-5	6-11	12-15	16-19
TYPICAL EXPOSURES						
FOOD - NATURAL	0.0004 - 0.14	0.0005 - 0.28	0.0004 - 0.23	0.0003 - 0.16	0.0002 - 0..1	0.0002 - 0..1
BREAST MILK BACKGROUND	0.0007 - 0.001					
SUM FOOD*	**0.14**	0.2800	0.2300	0.1600	0.1000	0.1000
CARB CLEANER - INHALATION	0.0003	0.0003	0.0002	0.0002	0.0001	0.0003
SPRAY PAINT - INHALATION	0.008	0.0070	0.0060	0.0050	0.0030	0.0080
WOOD STAIN - INHALATION	0.016	0.0140	0.0120	0.0100	0.0060	0.0160
PAINT THINNER LIQUID INHALATION	0.000059	0.0001	0.00005	0.00004	0.00002	0.0001
max PAINT THINNER CLEAN UP INHALATION	0.0013	0.0011	0.0010	0.0008	0.0005	0.0080
max PAINT THINNER DERMAL						0.0013
HOBBY ADHESIVE INHALATION	0.0004	0.0003	0.0003	0.0002	0.0004	0.0004
maxHOBBY ADHESIVE DERMAL						
ADULT ADHESIVE USE	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
HOBBY MODEL PAINT INHALATION	0.0006	0.0005	0.0004	0.0003	0.0006	0.0005
sum direct product use	0.026759	0.023353	0.020045	0.016626	0.010683	0.03467
PRODUCT + FOOD	0.166759	0.303353	0.250045	0.176626	0.110683	0.13467

*For infants, the higher of breast milk or food was used

Table 5. ANNUAL BASIS – Exposures in mg/kg/day by age group

	PASSIVE FOR < 16 AGES, ACTIVE FOR 16-19 EXCEPT HOBBY SCENARIOS - AGES 12-15 ALSO ACTIVE					
MAXIMUM EXPOSURES	<1	1-2	3-5	6-11	12-15	16-19
averageFOOD - NATURAL	0.0004 - 0.14	0.0005 - 0.28	0.0004 - 0.23	0.0003 - 0.16	0.0002 - 0..1	0.0002 - 0..1
BREAST MILK OCCUPATIONALLY EXPOSED MOTHER	0.16					
SUM FOOD*	0.16	0.2800	0.2300	0.1600	0.1000	0.1000
CARB CLEANER - INHALATION	0.0012	0.0010	0.0008	0.0007	0.0005	0.0012
SPRAY PAINT - INHALATION	0.0171	0.0153	0.0133	0.0105	0.0067	0.0058
WOOD STAIN - INHALATION	0.0261	0.0233	0.0202	0.0161	0.0102	0.0266
PAINT THINNER LIQUID INHALATION	0.000986301	0.0010	0.0007	0.0007	0.0003	0.0010
PAINT THINNER CLEAN UP INHALATION	0.0013	0.0011	0.0010	0.0008	0.0005	0.0080
PAINT THINNER DERMAL						0.0013
HOBBY ADHESIVE INHALATION	0.0011	0.0010	0.0009	0.0007	0.0013	0.0011
HOBBY ADHESIVE DERMAL						
ADULT ADHESIVE USE	0.002054795	0.0021	0.0016	0.0012	0.0008	0.0025
HOBBY MODEL PAINT INHALATION	0.00099726	0.0010	0.0009	0.0007	0.0011	0.0010

*For infants, the higher of breast milk or food was used