MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

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INTEROFFICE COMMUNICATION

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TO: File for Polyethylene glycol mono(octylphenyl)ether (CAS # 9036-19-5)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: July 8, 2021

SUBJECT: Screening Level for Polyethylene glycol mono(octylphenyl)ether (CAS # 9036-19-5)

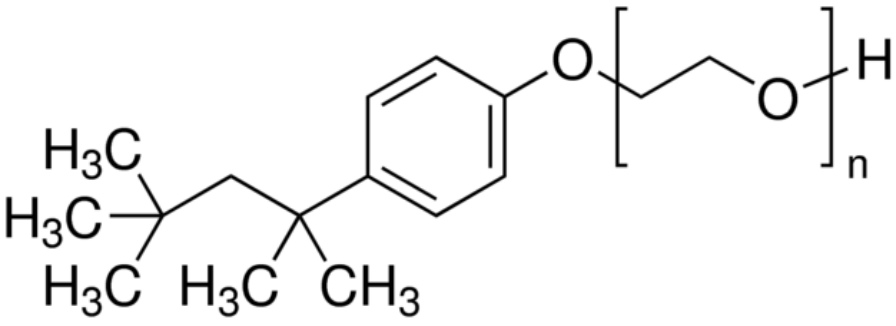
Summary

The initial threshold screening level (ITSL) for polyethylene glycol mono(octylphenyl)ether (CAS # 9036-19-5) is 1.9 µg/m^3 based on an annual averaging time.

Uses and Physical Chemical Properties

Polyethylene glycol mono(octylphenyl)ether is used as a non-ionic detergent and as a spermicide.

Table 1. Physical/Chemical Properties of Polyethylene glycol mono(octylphenyl)ether

Structure	
CAS Number	9036-19-5
Synonyms	α-[(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-poly(oxy-1,2-ethanediyl); octylphenol ethoxylate; **Octoxynol-9**; t-det c08
Appearance/Odor	Light yellow liquid
Molecular Weight	294.432 g/mol

Literature Search

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold limit Values (TLVs). International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched 10/28/2020), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), and the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR).

The European Chemicals Agency has listed polyethylene glycol mono(octylphenyl)ether (CAS # 9036-19-5) as a substance of very high concern and considers it an endocrine disruptor as polyethylene glycol mono(octylphenyl)ether degrades to 4-(1,1,3,3-tetramethylbutyl)phenol [4-tert-OP] (CAS# 140-66-9) a known endocrine disruptor (ECHA, 2012).

Studies

In a respiratory irritancy study by Alarie and Stock (EPA, 1996), 4 male Swiss Webster mice/dose were exposed head only to an aerosol in concentrations of 12, 22, 51, 118, or 134 mg/m^3 of a formulation containing an unknown amount of polyethylene glycol mono(octylphenyl)ether (CAS # 9036-19-5) for 180 minutes (no mention of control groups). Mice exposed to 118 and 134 mg/m^3 had clearly induced pulmonary irritation (characteristic pause between breaths). Mice exposed to 51 mg/m^3 had increased respiratory frequency. One animal exposed to 22 mg/m^3 had pulmonary irritation during the recovery period. Respiratory rate changes: a 3.4% decrease in respiratory rate at 12 mg/m^3; a 4.4% decrease in respiratory rate at 22 mg/m^3; a 12.5% decrease in respiratory rate at 51 mg/m^3; a 33.6% decrease in respiratory rate at 118 mg/m^3; and a 58.0% decrease in respiratory rate at 134 mg/m^3. Since the exact composition of the substance tested is not known, and as the percentage of polyethylene glycol mono(octylphenyl)ether is unknown, this study will not be used to derive a screening level. This study is only listed to show that the formulation containing polyethylene glycol mono(octylphenyl)ether as the principal ingredient can cause pulmonary irritation and a decrease in respiratory rate.

In a developmental study by Leung and Ballantyne (1999), pregnant CD rats (27 females/dose) were given either 0, 70, or 340 mg/kg-day octoxynol-9 (CAS # 9036-19-5) in their feed from gestation days 6-16, and on gestation day 17, were placed on untreated feed. All rats were sacrificed on gestation day 20. In dams, a statistically significant decrease in corpora lutea occurred at 70 and 340 mg/kg-day. A statistically significant decrease in implants occurred at 70 and 340 mg/kg-day. A statistically significant decrease in live implants occurred at 70 and 340 mg/kg-day. A statistically significant increase in dead implants occurred at 70 and 340 mg/kg-day. A statistically significant decrease in body weight gain occurred for gestation days 6-17 for 70 and 340 mg/kg-day. And a statistically significant decrease occurred in gravid uterine weight at 70 and 340 mg/kg-day.

In pups, there was a statistically significant increase in fetal body weight at 70 and 340 mg/kg-day. A statistically significant increase in the percentage of displaced testes occurred at 340 mg/kg-day. A statistically significant decrease resulted in poorly ossified 5th and/or 2nd metacarpals. A statistically significant increase occurred in vestigial 14th thoracic rib at 340 mg/kg-day. A statistically significant increase occurred in accessory ribs on cervical vertebra 7 at 340 mg/kg-day. A statistically significant increase occurred in both cervical and 14th thoracic rib at 340 mg/kg-day. A statistically significant decrease resulted in poorly ossified hyoid. Though not confirmed histologically, there was a statistically significant decrease in hydronephrosis (unilateral) at 70 and 340 mg/kg-

day and a statistically significant increase in hydronephrosis (bilateral) at 340 mg/kg-day. Hydronephrosis is the swelling of one or both kidneys and is associated with an inability of urine to drain from the kidney.

ITSL Derivation

The EPA Benchmark dose software [BMDS] (version 3.1.2) was used with dichotomous endpoints. Developmental studies generally use the nested dichotomous model. It was not possible to use the nested dichotomous models as litter specific data were not provided. The original data from the Leung and Ballantyne (1999) study were listed as percentages, which were converted to calculated number of pups for easier data entry into BMDS. Of all the statistically significant changes due to exposure to octoxynol-9, only four of the fetal variations produced statistically satisfactory results in BMDS. These critical effects are listed in Table 2. BMDS cannot resolve negative slopes, therefore the inverse of the data had to be used to produce a positive slope. Specifically, instead of a decrease, fetal poorly ossified hyoid in fetal pups had to be recalculated and changed to overly ossified hyoid. Fetal pup hyoid bone is normally poorly ossified to allow for bone growth. Calculated model predictions for significant fetal variations are listed in Table 3.

Table 2. Significant Fetal Variations in CD Rats Dosed with Octoxynol-9

	Dosage (mg/kg-day)		
Critical Effect	0	70	340
Displaced Testes	18/229	14/227	51/166
Accessory ribs on Cervical Vertebra 7	0/229	84/227	107/166
Skeletal Variation in both Cervical and 14th Thoracic Rib	0/229	0/227	83/166
Overly Ossified Hyoid	13/229	72/227	119/166
Fetal body weights (g)*	3.42±0.29	3.66±0.27	3.69±0.25

*Values are mean weights with ± standard deviations.

Table 3. Model Predictions for Significant Fetal Variations in CD Rats Dosed with Octoxynol-9						
Critical Effect	**Model**	**p-Value**	**Chi^2**	**AIC**	**Scaled Residual**	**BMDL**
Displaced Testes	Gamma	0.1576	1.9975	315.0929	3.594E-07	115.8581
Accessory ribs on Cervical Vertebra 7	Log-Logistic	0.1020	4.5649	521.6589	-0.0019	13.3645
Skeletal Variation in both Cervical and 14th Thoracic Rib	Gamma	0.9999	2.1250E-05	232.1249	6.684E-06	165.2416
Overly Ossified Hyoid	Gamma	0.1445	2.125	587.3812	-0.3849	24.0188
Fetal body weights (g)	N/A	N/A	N/A	N/A	N/A	N/A

Discussion

Fetal body weights change from normal are a sensitive indicator of developmental toxicity. It is concerning that fetal body weights, which are developmentally relevant endpoints and show statistically significant changes, were not amenable to benchmark dose modeling. The standard for body weight changes of 10% is significant, for fetal body weights 5% is significant. In this study, the change in fetal body weight exceeds 5% and is statistically significant. There is also a concern in that there are only two dose groups, which is the minimum dataset allowable for benchmark dose modeling. The BMDS most sensitive endpoint critical effect is the accessory ribs on cervical vertebra 7, which shows frank effects at the lowest dose. The benchmark dose modeling exercise does help to determine that there are effects below the lowest dose. The BMDS analysis can also be used as supporting information when using the statistically significant change in fetal body weights as the critical effect.

The EPA (2011) recommends the use of body weight ¾ ($BW^{¾}$) as the default method in the derivation of the oral reference dose (RfD). This methodology is used for calculating the dosimetric adjustment factor to determine the human equivalent dose for both cancer and non-cancer endpoints. RfDs are generally calculated based on subchronic or chronic studies (approximately 90 days or longer studies). The method is also best applied for adult animal to adult human extrapolations. Though EPA does state that data can be used to extrapolate for children ages 6 months to adult for certain endpoints. In this case, the use of the $BW^{¾}$ default is inappropriate for deriving a screening level for this study endpoint. The developmental study exposed pregnant CD rats between gestation days 6-16 (a total of 11 days). The critical effects were detected in the fetal pups. This study focused on the developmental effects on the offspring, not long-term effects of the adults. Therefore, $BW^{¾}$ dosimetric adjustment to determine the human equivalent dose will not be used in deriving a screening level for polyethylene glycol mono(octylphenyl)ether.

Potential ITSL Using the Benchmark Dose Software Results

If the screening level was derived from the BMDS results above, EPA (2012) states the p-value must be greater than 0.1, such that the greater the p-value the better the model fits the data. Also, the lower the Akaike Information Criterion (AIC) the better the model fits the available data. The AIC is used to compare different possible models to determine which model is the best fit for the data. The scaled residual must be less than 2 decimals away from 0, in either a positive or negative direction and is used to verify that the p-value is acceptable. The lower-bound confidence limit on the benchmark dose (BMDL) is the point of departure value determined by the model. If the available BMDLs are within 3-fold range, then the model with the lowest AIC is selected. If the BMDLs are not within 3-fold range, then the model with the lowest BMDL is selected.

Following the EPA (2012) criteria, the most critical effect would be the accessory ribs on cervical vertebra 7 with the corresponding BMDL of 13.3645 mg/kg-day. Since the exposure was between gestation days 6-16 (11 days average), the 7-day oral equation would be used to calculate the screening level using Rule 232(1)(e):

$$ITSL = \frac{NOAEL\ ({}^{mg}/_{kg-day})}{35\ \times 100} \times \frac{W_A}{I_A} \times \frac{b}{a}$$

Where:

W_A= Body weight of experimental animal in kilograms (kg).

I_A= Daily inhalation rate of experimental animal in cubic meters/day.

b = Absorption efficiency by the oral route of exposure.

a = Absorption efficiency by the inhalation route of exposure.

The W_A is the Sprague-Dawley CD rat control weight on gestation day 1 of 0.198 kg. The I_A is determined by the following equation taken from EPA (1988) determined below:

$$I_A = 0.80 \times W^{0.8206}$$

Where:

I = Inhalation rates in cubic meters/day.

W = Body weight (kg).

$$I_A = 0.80 \times 0.198^{0.8206} = 0.2118\ {}^{m^3}/_{day}$$

The value b/a is not known and therefore a default value of 1 is used. Using the above equation:

$$ITSL = \frac{13.3645\ ({}^{mg}/_{kg-day})}{35\ \times 100} \times \frac{0.198\ kg}{0.2118\ {}^{m^3}/_{day}} \times \frac{1}{1} = 0.0035696\ {}^{mg}/_{m^3} = 3.5696\ {}^{\mu g}/_{m^3}$$

$$\approx 3.6\ {}^{\mu g}/_{m^3}$$

ITSL Using the LOAEL for Change in Fetal Body Weight

The screening level will be based on the statistically significant critical effect of increase in fetal body weight at the lowest dose of 70 mg/kg-day. Using this dose as the LOAEL, and as stated above, since the exposure was between gestation days 6-16 (11 days), the 7-day oral equation would be used to calculate the screening level using Rule 232(1)(e):

$$ITSL = \frac{LOAEL\ (^{mg}/_{kg-day})}{35\ \times 100\ \times UF} \times \frac{W_A}{I_A} \times \frac{b}{a}$$

$$ITSL = \frac{70\ ^{mg}/_{kg-day}}{35 \times 100 \times 10} \times \frac{0.198\ kg}{0.2118\ ^{m^3}/_{day}} \times \frac{1}{1} = 0.001869688\ ^{mg}/_{m^3} = 1.869688\ ^{\mu g}/_{m^3}\ \approx 1.9\ ^{\mu g}/_{m^3}$$

Based on Rule 232(2)(c), the averaging time is annual. Established from the above data, the ITSL for polyethylene glycol mono(octylphenyl)ether is 1.9 µg/m^3 based on an annual averaging time.

References

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