MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Acrolein (CAS No. 107-02-8)

FROM: Michael Depa, Toxicologist, Air Quality Division

SUBJECT: Chronic Screening Level Update for Acrolein

DATE: October 5, 2022

The chronic Initial Threshold Screening Level (ITSL) for acrolein is 0.4 micrograms per cubic meter (µg/m³) with an annual averaging time. The previous chronic ITSL of 0.16 µg/m³ is being rescinded. The acute ITSL of 5 µg/m^3 with a 1-hour averaging time is retained and is not discussed further in this memo.

The chronic ITSL is derived from the California's Office of Environmental Health Hazard Assessment (OEHHA) chronic Recommended Exposure Level (REL) of 0.35 µg/m³. OEHHA (2008a) published an in-depth review of the toxicological literature on acrolein and provided detailed reasoning for the derivation of the REL. OEHHA based their chronic REL on a more recent toxicity study (Dorman et al., 2008) than the study the U.S. Environmental Protection Agency (EPA, 2003) used to derive their reference concentration (RfC), which was based on Feron et al. (1978). OEHHA's choice of study and methodology were determined to be more appropriate based on scientific reasoning than EPA's derivation of the RfC. The REL forms the basis of the ITSL, with rounding the REL value to one significant figure.

What follows is an excerpt from OEHHA's Technical Support Document for Acrolein Reference Exposure Levels (page 58-60):

> Chronic Toxicity to Experimental Animals
> Nasal and pulmonary effects following acrolein exposure for 13 weeks (6 hours/day, 5 days / week) were described by Dorman et al. (2008) in 360 male F344 rats. The whole-body exposures were to air concentrations of 0, 0.02, 0.06, 0.2, 0.6, and 1.8 ppm acrolein, with evaluation of respiratory tract histopathology after 4, 14, 30 and 65 days of exposure, and at 60 days following the end of the 13 week exposure. Body weights of all acrolein exposed rats were depressed but there were reportedly no other significant increases in clinical signs. Formalin fixed noses were sectioned transversely providing six sections of the nasal cavity at standard levels. Larynx, trachea and lungs were fixed, stained with hematoxylin and eosin, and examined histologically. The study examined both respiratory and olfactory epithelia with the former being the more sensitive as evidenced by inflammation, hyperplasia, and squamous metaplasia. Mild hyperplasia of the respiratory epithelia was first observed after 4 days of exposure to 0.6 ppm. The NOAEL for pathology of nasal respiratory epithelia was 0.2 ppm in the lateral walls of level II, and for olfactory epithelia, 0.6 ppm. At the highest concentration, 1.8 ppm, mild squamous metaplasia was also observed in the larynx and trachea, but no treatment related effects were seen in the lungs. Two months following cessation of exposure, only partial recovery of the olfactory epithelium was observed; primarily in caudal areas where lesions developed more slowly and were less severe.

Schroeter et al. (2008) used data from the above study by Dorman et al. (2008) for the development of a physiological computational fluid dynamics (CFD) model of acrolein nasal dosimetry. The CFD models of Kimbell et al. (1997) and Subramaniam et al. (1998) were modified to estimate kinetic parameters of acrolein flux in rat nasal passages, and allow a cross species prediction of acrolein flux in humans associated with histopathology. Based on a NOAEL of 0.6 ppm and a LOAEL of 1.8 ppm for olfactory neuronal loss from Dorman et al. (2008), the CFD model predicted a threshold acrolein flux of 72 pg/cm^2-s at region 11, comprising portions of the third ethmoturbinate. Assuming equal tissue doses of acrolein elicit similar responses in the olfactory epithelium of rats and human, an exposure level that may be expected to represent the threshold for olfactory neuronal loss in humans may be estimated. The 99th percentile olfactory flux value that is equal to the threshold of 72 pg/cm^2-s was estimated to be 45 ppb. The authors use this concentration to estimate a human equivalent NOAEL of 8 ppb, and a reference concentration (RfC) of 0.27 ppb. However, the threshold acrolein flux associated with the lower NOAEL of 0.2 ppm, reported by Dorman et al. (2008) for respiratory epithelium, was not estimated, and an equivalent human threshold and NOAEL is not available. The rationale for this, presented in Dorman et al. (2008), is “Our CFD modeling efforts have revealed that although the observed NOAEL for the respiratory epithelium is lower than that seen for the olfactory epithelium (i.e., 0.2 vs. 0.6 ppm), in actuality the olfactory epithelial lesion arises at an appreciably lower delivered tissue dose suggesting that the olfactory epithelium is more sensitive to the effects of inhaled acrolein than is the respiratory epithelium (Schroeter et al. (2008).” The RfC of 0.27 ppb estimated by the authors is thus based on lesion formation at the lowest modeled tissue dose rather than on the more relevant value of the lowest applied acrolein concentration associated with an adverse effect.

Structural and functional changes in the respiratory tract were also examined in male Fischer-344 rats exposed for 6 hours/day, 5 days/week for 62 days to acrolein at concentrations of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3)(Kutzman, 1981; Kutzman et al., 1985). Each group of 24 animals was assessed for pulmonary function immediately prior to the end of the experiment. Pulmonary function tests included lung volumes, forced respiratory capacity, pulmonary resistance, dynamic compliance, diffusing capacity of carbon monoxide, and multi-breath nitrogen washout. At the end of the experiment, animals were killed and histopathological changes in the lungs were recorded. Eight additional rats were designated for histopathology and 8 rats were used for reproductive testing only. All analyses were performed at 6 days postexposure to minimize the acute effects of acrolein. Mortality was high (56%) in rats exposed to 4.0 ppm (9.2 mg/m^3). The observed mortality was due to acute bronchopneumonia in these cases. The animals from this group that survived had reduced body weight. No histological changes were observed in extra-respiratory tissues in any group. There was a concentration dependent increase in histological changes to the nasal turbinates (increased submucosal lymphoid aggregates), beginning at 0.4 ppm. Concentration-dependent damage to the peribronchiolar and bronchiolar regions included epithelial necrosis and sloughed cells lying free in the lumen. No lung lesions were observed in the 0.4 ppm group. The LOAEL for nasal lesions (squamous epithelial metaplasia and neutrophil infiltration) in this study was 0.4 ppm.

Feron et al. (1978) exposed groups of 20 Syrian golden hamsters, 12 SPF Wistar rats and 4 Dutch rabbits (of both sexes) to acrolein vapor at 0, 0.4, 1.4 and 4.9 ppm (0, 0.92, 3.2, and 11.3 mg/m^3) 6 hours/day, 5 days/week for 13 weeks. The most prominent effects at the highest level included mortality in rats (3 of each sex), and ocular and nasal irritation, growth depression, and histopathological changes of the respiratory tract in each species. The changes in the airways induced by acrolein consisted of destruction, and hyperplasia and metaplasia of the lining epithelium accompanied by inflammatory alterations. Rats were the most susceptible species examined and showed treatment-related histopathological abnormalities in the nasal cavity down to 0.4 ppm (LOAEL), whereas this level was a NOAEL in hamsters and rabbits. The results for individual rats at 0.4 ppm were not given.

Bouley et al. (1975; 1976) exposed male SPF OFA rats continuously to 0.55 ppm (1.3 mg/m^3) of acrolein for up to 63 days. This level of acrolein led to a greater susceptibility to airborne Salmonella enteritidis infection during the first three weeks compared to control rats but it disappeared spontaneously when exposure was continued beyond three weeks. The general toxic effect of diminished weight gain (due to reduced feeding) compared to the control group

lasted as long as exposure and disappeared only after acrolein was discontinued. Sneezing, a sign of nasal irritation, was consistently observed in the exposed animals on days 7 through 21 but ceased thereafter. No histopathology of the nasal cavity of or any other tissue was reported. In one of the few chronic studies reported, Feron and Kruysse (1977) exposed hamsters (18/gender) to 4 ppm (9.2 mg/m^3) acrolein for 7 hours/day, 5 days/week, for 52 weeks. Mild to moderate histological changes were observed in the upper and lower respiratory tract. No evidence of toxicity to other organs was apparent at necropsy, although body weight was decreased. Hematology, urinalysis, and serum enzymes were not affected by exposure. Thus 4 ppm is a chronic LOAEL for hamsters. As noted above, hamsters appear to be a less sensitive species than rats (Feron et al., 1978).

Exposures of rodents have generally formed the basis for the determination of acrolein's chronic effects. However, an interspecies comparison was conducted by Lyon and associates (Lyon et al., 1970) who investigated the effects of repeated or continuous exposures of acrolein on Sprague-Dawley rats (n = 15/exposure group), guinea pigs (n = 15), beagle dogs (n = 2), and male squirrel monkeys (n = 9). Animals were exposed to 0.7 or 3.7 ppm (1.6 or 8.5 mg/m^3) acrolein for 8 hours/day, 5 days/week, for 6 weeks, or continuously to 0.22, 1.0, or 1.8 ppm (0.5, 2.3, or 4.1 mg/m^3) for 90 days. The results below suggest that dogs and monkeys were more susceptible to acrolein's effects than were the rodents.

Two monkeys in the 3.7 ppm intermittent exposure group died within 9 days. Monkeys and dogs salivated excessively during the first week. Squamous metaplasia and basal cell hyperplasia of the trachea were observed in monkeys and dogs; 7 of the 9 monkeys repeatedly exposed to 3.7 ppm also exhibited bronchiolitis obliterans with squamous metaplasia in the lungs. Bronchopneumonia was noted in the dogs. Inflammation in the lung interstitiae was more prominent in the dogs than in the monkeys. Rats and guinea pigs did not exhibit signs of toxicity when exposed intermittently to 3.7 ppm. Continuous exposure to 1.0 and 1.8 ppm, but not 0.22 ppm acrolein, resulted in salivation and ocular discharge in the monkeys and dogs. Rats and guinea pigs appeared normal at all concentrations. Rats exhibited significant weight loss in the 1.0 and 1.8 ppm continuous exposure groups. Nonspecific inflammatory changes were observed in sections of brain, heart, lung, liver and kidney from all species exposed to 1.8 ppm. The lungs from the dogs showed confluent bronchopneumonia. Focal histological changes in the bronchiolar region and the spleen were detected at 0.22 ppm in dogs. Nonspecific inflammatory changes at the 0.22 ppm level were apparent in liver, lung, kidney and heart from monkeys, guinea pigs and dogs. Unfortunately, the nasal cavity was not examined in this study. While there were no unexposed control animals for any species, the cross-species comparison shows substantial interspecies variability in susceptibility.

Important information about the derivation of the Dosimetric Adjustment Factor (DAF) is provided here (from page 64 of OEHHA, 2008a):

The DAF is a factor derived by OEHHA based on the modeled comparative flux of formaldehyde in the upper respiratory tracts of rats, rhesus monkeys and humans by Kimbell et al. (2001) (see Section 4.4.7.2.2 of the TSD). Kimbell et al. used three-dimensional, anatomically realistic, computational flow dynamic models to estimate mass flux across 20 consecutive bins representing the nasal passages. The mean flux at each bin was weighted by the percent of non-squamous epithelium in that bin to derive a weighted average flux for each bin. Averaging across all 20 bins provides an overall estimate of the flux for comparison between species (rat, 13.63 pmol/mm^2; human, 30.80 pmol/mm^2). Peak flux values were also estimated for the rat (2620 pmol/mm^2) and human (2082 pmol/mm^2), and averaged with the mean flux values to estimate the DAF (0.85). The DAF is the ratio of this value for the rat to that for humans. Although acrolein is more reactive than formaldehyde, both compounds appear to have their effects primarily on the respiratory (vs. olfactory) epithelium (Cassee et al., 1996a). This supports the assumption that in applying the DAF to acrolein, acrolein and formaldehyde deposit similarly in the nasal passages. In the absence of acrolein-specific modeling data, any residual uncertainty associated with this assumption is reflected in the use of an interspecies UFA-k of 2.

OEHHA (2008a) provided detailed information used to calculate the chronic REL for acrolein (see Table 1.)

Table 1. Data Used to Calculate the Chronic Reference Exposure Level for Acrolein

Study	Dorman et al., 2008
Study population	360 adult Fischer-344 rats
Exposure method	Discontinuous whole body 0.02 – 1.8 ppm
Exposure	Continuity 6 hours/day, 5 days/week
Exposure duration	65 days
Critical effects	Lesions in the respiratory epithelium
LOAEL	0.6 ppm (1.38 mg/m³)
NOAEL	0.2 ppm (0.459 mg/m³)
Benchmark concentration	Not derived
Time-adjusted exposure (to continuous exp.)	36 ppb (0.0819 mg/m³) = 0.2 ppm × 6/24 × 5/7 0.0819 mg/m³ = 0.459 mg/m^3 × 6/24 × 5/7
Dosimetric Adjustment Factor (DAF)	0.85
Human Equivalent Concentration (HEC)	30 ppb = 36 ppb × 0.85 (DAF) 0.0696 mg/m³ = 0.0819 mg/m³ × 6/24 × 5/7
LOAEL uncertainty factor (UFL)	1 (NOAEL observed)
Subchronic uncertainty factor (UFs)	3 (exposure 8-12% of lifetime)
Interspecies uncertainty factor	
Toxicokinetic (UFA-k)	2 (DAF adjustment based on analogue chemical)
Toxicodynamic (UFA-d)	3 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UFH-k)	1
Toxicodynamic (UFH-d)	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	200
Reference Exposure Level	0.35 µg/m³ (0.15 ppb)

The observation of a NOAEL eliminates the need for a UF for the LOAEL to NOAEL conversion. Time adjustment from the experimental to continuous exposure gave 36 ppb (0.2 ppm × 6 hr/24 hr × 5 days/7 days). A DAF of 0.85 gave an equivalent human exposure of 30 ppb. Use of the DAF for an analogue chemical (formaldehyde) entails an uncertainty factor of 2 according to OEHHA policy (OEHHA, 2008b). The resulting cumulative UF of 180 rounded to one significant figure of 200 yields OEHHA's chronic REL of 0.35 µg/m³ (0.15 ppb). AQD is adopting the REL as the ITSL; however, the value is rounded to one significant figure such that the ITSL equals 0.4 µg/m³. Annual averaging time is applicable to the ITSL since a UF of 3 was used to extrapolate to chronic exposures from a subchronic duration animal study.

References

Cassee FR, Arts JH, Groten JP and Feron VJ (1996a). Sensory irritation to mixtures of formaldehyde, acrolein, and acetaldehyde in rats. Arch Toxicol 70(6): 329-37.

Dorman DC, Struve MF, Wong BA, Marshall MW, Gross EA and Willson GA (2008). Respiratory tract responses in male rats following subchronic acrolein inhalation. Inhal Toxicol 20(3): 205-16.

EPA. 2003. Toxicological Review of Acrolein (CAS No. 107-02-8). In Support of Summary Information on the Integrated Risk Information System (IRIS). May 2003. US Environmental Protection Agency. Washington, DC. EPA/635/R-03/003. 106 pages. PDF Downloaded October 5, 2022. https://iris.epa.gov/static/pdfs/0364tr.pdf

Feron, VJ; Kryusse, A; Til, HP; *et al*. 1978. Repeated exposure to acrolein vapor: subacute studies in hamsters, rats and rabbits. Toxicology 9:47-57.

Kimbell JS, Godo MN, Gross EA, Joyner DR, Richardson RB and Morgan KT (1997). Computer simulation of inspiratory airflow in all regions of the F344 rat nasal passages. Toxicol Appl Pharmacol 145(2): 388-98.

Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT, Conolly RB and Miller FJ (2001). Dosimetry modeling of inhaled formaldehyde: Binning nasal flux predictions for quantitative risk assessment. Toxicological Sciences 64(1): 111-121.

Kutzman R. (1981). A subchronic inhalation study of Fischer 344 rats exposed to 0, 0.4, 1.4, or 4.0 ppm acrolein. National Toxicology Program: Interagency Agreement No. 222-Y01-ES-9-0043. Brookhaven National Laboratory. Upton, NY

Kutzman RS, Popenoe EA, Schmaeler M and Drew RT (1985). Changes in rat lung structure and composition as a result of subchronic exposure to acrolein. Toxicology 34(2): 139-51.

Lyon JP, Jenkins LJ, Jr., Jones RA, Coon RA and Siegel J (1970). Repeated and continuous exposure of laboratory animals to acrolein. Toxicol Appl Pharmacol 17(3): 726-32.

OEHHA. 2008a. Technical Supporting Document for Noncancer RELs, Appendix D1. Updated July 2014. California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA). Acrolein. Pages 47-74. Downloaded PDF October 4, 2022. https://oehha.ca.gov/media/downloads/crnr/appendixd1final.pdf

OEHHA. 2008b. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Air Toxics Hot Spots Risk Assessment Guidelines. June 2008. Air Toxicology and Epidemiology Branch. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. 1515 Clay Street, 16th Floor. Oakland, California 94612. Downloaded October 5, 2022. https://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf

Schroeter JD, Kimbell JS, Gross EA, Willson GA, Dorman DC, Tan YM and Clewell HJ, 3rd (2008). Application of physiological computational fluid dynamics models to predict interspecies nasal dosimetry of inhaled acrolein. Inhal Toxicol 20(3): 227-43.

Subramaniam RP, Morris JB and Ultman, JS Frederick CB, Bush ML, Lomax LG, Black KA, Finch L, Kimbell JS, Morgan KT, (1998). Application of a hybrid computational fluid dynamics and physiologically based inhalation model for interspecies dosimetry extrapolation of acidic vapors in the upper airways. Toxicol Appl Pharm 152(1): 211-231.

MD:lh