# Appendix H - Derivation of AGCs for Aldehyde Compounds

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M E M O R A N D U M

To: File

From: Steven De Santis, Research Scientist III

Subject: Aldehyde Compounds Without Health-based Concentration Values Detected During the Study Period of the Tonawanda Air Quality Community Monitoring Grant

Date: June 15, 2009

Aldehyde compounds were measured and detected at all four sites during the year long Tonawanda Air Quality Community Monitoring Study (Study). For all compounds measured during the Study, a risk classification scheme was derived based upon the percent of measured values above the method detection limit (MDL). Those compounds falling in Category A were detected less than fifty percent of the time and were classified as not being able to have their risk characterized. Compounds in Category B were detected above the MDL greater than fifty percent of the time and less than seventy-five percent of the time. The risk associated with compounds in Category B will be estimated and reported. Category C compounds were detected greater than the MDL more than seventy-five percent of the time and the risk will be quantified. For a complete description of this methodology, see the Section *"Suitability of the ambient data for data analysis and health risk evaluation"* found in Section 7.0 of the Final Report.

Several aldehyde compounds falling into Categories B and C did not have AGC (Annual Guideline Concentrations) concentration values adopted or derived by the Department. Table1 lists all the aldehyde compounds found in Category B and C with their AGCs. Currently, there are no AGCs for benzaldehyde, butyraldehyde and hexanal.

The AGC listed for formaldehyde in the 2007 AGC/SGC Tables is based upon a cancer endpoint and the Integrated Risk Information System (IRIS) does not support a non-cancer inhalation Reference Concentration (RfC) for formaldehyde. In December of 2008, California's Office of Environmental Health and Hazard Assessment published a Reference Exposure Level of 9.0 $\mu g/m^3$ published for formaldehyde. The Department recognizes this concentration value as the non-cancer health-based concentration.

Aldehydes can be described as unsaturated, saturated, linear and/or cyclic chemical compounds. The low molecular weight aldehydes, the halogenated aliphatic aldehydes, and the unsaturated aldehydes are the most irritating (1). Unsaturated aldehyde compounds possess a double bond along with the R-C-O-H aldehyde structure. The irritating inhalation health effects of the unsaturated compounds, acrolein and crotanaldehyde are well documented. Low molecular weight compounds such as formaldehyde and acetaldehyde are also well documented for their irritating inhalation health effects and their non-cancer health based concentration values are listed in Table 1.

**Table 1** Category B & C Aldehydes Non-cancer RfC

| | | Non-cancer RfC | Reference |
|---|---|---|---|
| **CAS#** | **Compound** | **(µg/m3)** | **Agency** |
| 000050-00-0 | Formaldehyde | 9.8 | ATSDR |
| 000066-25-1 | Hexanal | NA | |
| 000075-07-0 | Acetaldehyde | 9 | IRIS |
| 000100-52-7 | Benzaldehyde | NA | |
| 000107-02-8 | Acrolein | 0.02 | IRIS |
| 000110-62-3 | Valeraldehyde | 420 | OEHHA |
| 000123-38-6 | Propionaldehyde | 8 | IRIS |
| 000123-42-8 | Butyraldehyde | NA | |

ATSDR – Agency for Toxic Substance Disease Registry
IRIS - Integrated Risk Information System
OEHHA - Office of Environmental Health Hazard Assessment - California

As an indication of the acute relative potency of compounds within a class, a review comparing of the lethal dose-50 ($LD_{50}$) or the lethal concentration-50 ($LC_{50}$) can be performed. Table 2 below lists the $LD_{50}$ and $LC_{50}$ for the compounds meeting the requirements of Category B and C of the Study.

**Table 2** Category B & C Aldehydes LC50 and LD50 Values

| CAS# | Compound | Molecular Weight | Molecular Formula | LC50 (mg/m3) | LD50 (mg/kg) | Route | Species |
|---|---|---|---|---|---|---|---|
| 000050-00-0 | Formaldehyde | 30.03 | CH2O | | 100 | oral | Rat |
| | | | | 590 | | inhalation | Rat |
| 000075-07-0 | Acetaldehyde | 44.06 | C2H4O | | 661 | oral | Rat |
| 000123-38-6 | Propionaldehyde | 54.50 | C3H2O | | 1410 | oral | Rat |
| | | | | 21,800 | | inhalation | Mouse |
| 000107-02-8 | Acrolein* | 56.06 | C2H4O | | 46 | oral | Rat |
| | | | | 300 | | inhalation | Rat |
| 004170-30-3 | Crotanaldehyde* | 70.09 | C4H6O | | 206 | oral | Rat |
| 000123-42-8 | n-Butyraldehyde | 72.12 | C4H8O | | 2490 | oral | Rat |
| | | | | 44,610 | | inhalation | Mouse |
| 000110-62-3 | Valeraldehyde | 86.15 | C5H10O | | 4581 | oral | Rat |
| 000066-25-1 | Hexanal | 100.18 | C6H12O | | 4890 | oral | Rat |
| 000100-52-7 | Benzaldehyde | 106.13 | C7H6O | | 1300 | oral | Rat |
| | | | | 200 | | inhalation | Rat |

* - unsaturated compounds

As shown in Table 2, the lower molecular weight and unsaturated compounds have the lowest lethal acute concentration values. As the compounds' molecular weight increases for aliphatic compounds, the acute toxicity of the compound decreases. Benzaldehyde, an aromatic aldehyde, did show a greater lethal acute concentration than the lower molecular weight compounds.

A paper submitted by Babiuk, et. al. to the Journal of Toxicology and Applied Pharmacology (2), attempted to determine if sensory irritation to laboratory rats could be decreased with a preliminary exposure to other irritating substances. The usefulness of this paper is that the researchers' control were laboratory animals with no previous exposures to respiratory irritants. The sensory irritation response in these animals was quantified by measuring respiratory rate depression in a head-only inhalation chamber. The researchers were trying to discern the concentration eliciting a 50% decrease in respiratory rate ($RD_{50}$). The results of their study showed that the aldehydes tested produced $RD_{50}$ values which spanned 3 orders of magnitude. The unsaturated aliphatic aldehydes, acrolein and crotanaldehyde, produced an $RD_{50}$ of a 6 and 23 ppm respectively. The cyclic aldehydes had a $RD_{50}$ ranging from 600 to 1000 ppm while the least potent irritants were the saturated aliphatic aldehydes, acetaldehyde, propionaldehyde and butyraldehyde with $RD_{50}$ values 3000 to 6800 ppm.

Benzaldedhyde was part of a 2-Year National Toxicology Program (NTP) cancer study where male mice were given 0, 200, or 400 mg/kg benzaldehyde in corn oil by gavage, 5 days per week for 103 weeks and female mice were administered 0, 300, or 600 mg/kg benzaldehyde for 103 weeks. No significant differences in survival or body weight loss was observed between any of the groups of mice. The only effects of benzaldehyde were those seen in the forestomach of mice. The incidences of uncommonly occurring cell papillomas of the forestomach in both exposure groups were significantly greater than those in the controls, (1/50; low dose, 2/50; high dose, 5/50; female: 0/50; 5/50; 6/50). Also increased incidences of papillomas were observed by dose related increases in the incidences in forestomach hyperplasia (male: 7/50; 8/50; 16/50; female 12/50; 23/50; 39/50). The two year study concluded there was some evidence of carcinogenic activity of benzaldehyde for male or female mice, as indicated by the increased incidences of cell papillomas and hyperplasia of the fore stomach (3).

**Recommendation:**

Several aldehyde compounds falling into Categories B and C did not have Annual Guideline Concentrations values adopted or derived by the Department. Currently, there are no AGCs for benzaldehyde, butyraldehyde and hexanal.

The first approach to assigning an interim AGC is to choose the lowest AGC concentration in the chemical class and assign this concentration value to the unknown compound. In the case of aldehydes, the lowest annual guideline concentration is for formaldehyde. The AGC value for formaldehyde is based upon an inhalation cancer unit risk value set at a one-in-one-million excess cancer rate. The AGC value for acetaldehyde was established with the same procedure. The three compounds being evaluated do not have clear evidence that their adverse health effects are cancer related. Benzaldehyde was evaluated for its ability to elicit cancer in the NTP study but this was an ingestion study and it was not clearly

established that the inhalation of benzaldehyde would produce cancer in test animals and/or humans. Due to these concerns, the interim AGC assignments for the three compounds will be evaluated for non-cancer health effects.

Interim AGC Assignment:

Aldehydes can be described as unsaturated, saturated, linear and/or cyclic chemical compounds. Based upon the data in the literature cited, acute irritation health effects can be associated with the aldehyde chemical type.

For the three compounds currently without an AGC (benzaldehyde, butyraldehyde and hexanal) an interim AGC will be assigned as shown in Table 3. None of these compounds are unsaturated aldehydes so it is inappropriate for them to be compared to acrolein. The non-cancer reference concentration established by IRIS for acetaldehyde is the best fit compound for these unevaluated aldehydes. For the interim AGC concentration for butyraldehyde and hexanal, it is suggested the AGC established for acetaldehyde be used with a correction for molecular weight. This practice is currently employed in the AGC/SGC tables for other aliphatic compounds. The cyclic compound, benzaldehyde was found to elicit a greater $RD_{50}$ response in the research by Babiuk, et. al. and the NTP study suggested a potential for carcinogenic activity for ingestion so it is recommended to compare this compound to acetaldehyde but not adjust the comparison by the molecular weight.

**Table 3** Interim AGC Concentration Values

| | | **Non-cancer RfC** | **Reference** |
|---|---|---|---|
| **CAS#** | **Compound** | **(µg/m3)** | **Agency** |
| 000050-00-0 | Formaldehyde | 9.8 | ATSDR |
| 000066-25-1 | Hexanal | 20.0 | Interim AGC |
| 000075-07-0 | Acetaldehyde | 9 | IRIS |
| 000100-52-7 | Benzaldehyde | 9 | Interim AGC |
| 000107-02-8 | Acrolein | 0.02 | IRIS |
| 000110-62-3 | Valeraldehyde | 420 | TLV/420 |
| 000123-38-6 | Propionaldehyde | 8 | IRIS |
| 000123-42-8 | Butyraldehyde | 15.0 | Interim AGC |
| 004170-30-3 | Crotanaldehyde | NA | |

TLV/420 - Threshold Limit Value divided by safety factor of 420.

**References:**

(1) Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982

(2) Babiuk, C; Steinhagen, W.H; and Barrow, C.S.; Sensory Irritation to Inhaled Aldehydes after Formaldehyde Pretreatment, Toxicology and Applied Pharmacology, Vol 79, 143-149 1985

(3) National Toxicology Program NTP; Toxicology and Carcinogenesis Studies of Benzaldehyde in F344/N Rats and B6C3F1 Mice (Gavage Studies) p.3 (1988) Technical Rpt Series No. 378 NIH Pub No. 88-2588