MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Di-(2-ethylhexyl)phthalate (DEHP) [CAS# 117-81-7]

FROM: Doreen Lehner

SUBJECT: Screening Level Determination for Di-(2-ethylhexyl)phthalate (DEHP) [CAS# 117-81-7]

DATE: March 3, 2014

There was previously no Initial Threshold Screening Level (ITSL) for di-(2-ethylhexyl) phthalate (DEHP). The ITSL is now being established at 70 µg/m^3 based on an annual averaging time. The Initial Risk Screening Level (IRSL) was established on 12/2/1981 at 0.2 µg/m^3 based on an annual averaging time. The IRSL is being changed at this time to 0.61 µg/m^3 based on an annual averaging time and is based on a Water Resources Division literature review and derivation of a human oral carcinogenicity slope factor of 0.005745 (mg/kg/day)$^{-1}$. This is based on an increase in hepatocellular carcinomas / neoplastic nodules in an NTP (1982) study in male B6C3F1 mice exposed via diet for 103 weeks.

DEHP is an organic compound with a low vapor pressure and a molecular weight of 390.56 g/mol. It is one of the class of phthalate esters and is a colorless, viscous liquid that is soluble in oil, but not in water. Due to the low cost of production, DEHP is widely used in the manufacturing of articles made of polyvinylchloride (PVC). Plastics may contain 1 – 40% DEHP. DEHP is also used: as a hydraulic fluid and as a dielectric fluid in capacitors; and as a solvent in glowsticks. “The Food and Drug Administration (FDA) permits the use of DEHP-containing packaging only for foods that primarily contain water” (Wikipedia, 2014).

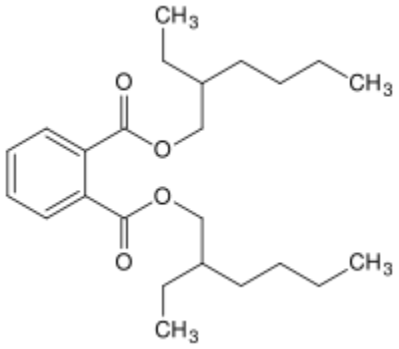

Figure 1. Chemical structure of DEHP.

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) - Online (searched 10/8/2012), National Library of Medicine, and the EPA Aggregated Computational Toxicology Resource (ACToR) Database.

IRSL Discussion and Derivation

The EPA (2013) has not established a reference concentration, but has established a reference dose of 0.02 mg/kg/day for DEHP. DEQ Water Resources Division (WRD) has an RfD of 0.019 mg/kg/day based on a LOAEL of 19 mg/kg/day for increased liver weight in female guinea pigs exposed via the diet for one year (Carpenter et al., 1953). This is the same basis as used by the EPA in deriving their RfD. Both WRD and the EPA used an uncertainty factor (UF) of 1,000 (10 for intraspecies, 10 for interspecies, and 10 for subchronic to chronic). WRD also has a human oral carcinogenicity slope factor of 0.005745 $(mg/kg/day)^{-1}$ which was derived in 1997 and modified in 2014; it is based on an increase in hepatocellular carcinomas/neoplastic nodules in a NTP (1982) study in male B6C3F1 mice exposed via diet for 103 weeks. Appendix A contains the WRD calculations for DEHP.

DEQ Remediation and Redevelopment Division (RRD) has an RfD of 0.019 mg/kg/day based on the DEQ-WRD RfD for DEHP. RRD also has a human oral carcinogenicity slope factor of 0.0032 $(mg/kg/day)^{-1}$ based on the same NTP (1982) study used by WRD in their 1997 assessment (prior to WRD's 2014 modification).

Additionally, the EPA (2013) classifies DEHP as B2 – Probable Human Carcinogen, and has calculated an oral cancer slope factor, but not an inhalation unit risk factor. The EPA (2013) has an oral slope factor of 0.014 $(mg/kg/day)^{-1}$ and a drinking water unit risk of 4.0 E-07 $(\mu g/L)^{-1}$. The oral slope factor is based on an NTP (1982) chronic study in which, "50 male and 50 female Fisher 344 rats per group were fed diets containing 0, 6000, or 12000 ppm DEHP for 103 weeks. Similarly, groups of 50 male and 50 female B6C3F1 mice were given 0, 3000, or 6000 ppm DEHP in the diet for 103 weeks. Animals were killed and examined histologically when moribund or after 105 weeks. No clinical signs of toxicity were observed in either rats or mice. A statistically significant increase in the incidence of hepatocellular carcinomas and combined incidence of carcinomas and adenomas were observed in female rats and both sexes of mice. The combined incidence of neoplastic nodules and hepatocellular carcinomas was statistically significantly increased in the high-dose male rats. A positive dose response trend was also noted" (EPA, 2013).

Rule 231(1) is used to develop an IRSL for DEHP. The equation is below:

$$IRSL = \frac{1 \times 10^{-6}}{unit\ risk}$$

The WRD human oral cancer value of 0.005745 $(mg/kg/d)^{-1}$ found in the worksheet in Appendix A is converted to an inhalation cancer value using the equation in Rule 231(3)(f), below:

$$q_1^*({}^{\mu g}/_{m^3})^{-1} = q_1^*({}^{mg}/_{kg/day})^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{a}{b}$$

$$q_1^* \left({}^{\mu g}/_{m^3}\right)^{-1} = 0.005745 \left({}^{mg}/_{kg/day}\right)^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{1}{1}$$
$$= 0.000001641 \left({}^{\mu g}/_{m^3}\right)^{-1}$$

Using this value for the unit risk gives:

$$IRSL = \frac{1 \times 10^{-6}}{0.000001641} = 0.609384522\ {}^{\mu g}/_{m^3} = 0.61\ {}^{\mu g}/_{m^3}$$

ITSL Discussion and Derivation

Even though there is no EPA RfC for DEHP in IRIS, EPA (2013) does have an oral RfD of 0.02 mg/kg/day, based on the Carpenter et al. (1953) guinea pig subchronic oral bioassay LOAEL of 0.04% diet (19 mg/kg bw/day) based on increased relative liver weight. The Carpenter et al., (1953) oral guinea pig study fed diets containing DEHP for a period of one year: 24 males and 23 females consumed feed containing 0.13% DEHP (64 mg/kg bw/day); 23 males and 23 females consumed feed containing 0.04% DEHP (19 mg/kg bw/day); and 24 males and 22 females were fed the control diet. No treatment related effects were observed on mortality, body weight, kidney weight, or gross pathology and histopathology of kidney, liver, lung, spleen, or testes. Statistically significant increases in relative liver weights were observed in both groups of treated females (64 and 19 mg/kg bw/day). The LOAEL in guinea pigs was determined to be 19 mg/kg/day. The EPA used an uncertainty factor of 1,000 (10 for interspecies variation, 10 for sensitive populations, and 10 for subchronic to chronic).

ATSDR (2002) has no inhalation Minimal Risk Level (MRL) for DEHP due to inadequate data for inhalation exposure. An intermediate-duration oral exposure (15 – 364 days) MRL of 0.1 mg/kg/day was derived for DEHP based on a no-observed-adverse-effects level (NOAEL) of 14 mg/kg/day for decreased fertility in a mouse reproductive study (Lamb et al., 1987). “A continuous breeding protocol was used in which pairs of mice were exposed to DEHP in the diet at doses of 0, 14, 140, or 420 mg/kg/day for up to 126 days. There were 20 breeding pairs in each exposed group and 40 pairs in the control group. No reproductive effects were observed at 14 mg/kg/day. Fertility was reduced at 140 mg/kg/day, as shown by reductions in number of litters per pair, number of live pups per litter, and proportion of live pups, indicating that this dose is the lowest-observed-adverse-effects level (LOAEL). Exposure to 420 mg/kg/day caused complete infertility during the continuous breeding part of the study (0/18 fertile pairs). Fertility was also profoundly reduced in crossover mating trials conducted in the 420 mg/kg/day mice (lower doses not tested) at the end of the continuous breeding phase of the study. The crossover study involved mating high dose mice of each sex to unexposed mice of the opposite sex to determine the affected sex; near to complete infertility occurred in both sexes (0/16 fertile females and 4/20 fertile males). Other effects included reduced combined testis, epididymis, and prostate weights, and reduced percentages of motile sperm and abnormal sperm, and reduced sperm concentration in the males, and reduced combined weight of ovaries, oviducts, and uterus in the females. Essentially all of the high-dose males had some degree of bilateral atrophy of the seminiferous tubules, but no exposure-related reproductive histopathology was observed in the females. Considering the reduced fertility and reproductive organ weights in the high-dose females, there is evidence that reproductive performance was impaired in both sexes

at 420 mg/kg/day. Because the crossover mating study was only conducted at the high dose level, the reduced fertility observed at the 140 mg/kg/day LOAEL is not necessarily due to reproductive toxicity in both sexes" (ATSDR, 2002).

ATSDR (2002) also has a chronic-duration oral exposure (> 365 days) MRL of 0.06 mg/kg/day based on a NOAEL of 5.8 mg/kg/day for testicular pathology in male rats from a comprehensive chronic toxicity study (David et al., 2000). "Groups of 50-80 rats of both sexes were fed DEHP in the diet for up to 104 weeks. Reported average daily doses were 0, 5.8, 29, 147, or 789 mg/kg/day in males and 0, 7.3, 36, 182, or 939 mg/kg/day in females. End points evaluated in all dose groups included clinical observations, food consumption, body and organ weights, and clinical pathology indices. Necropsy and histological examinations included the control and two highest dose groups after 78 weeks, the control and high-dose groups after 104 weeks, and target tissues and gross lesions from the remaining dose groups after 104 weeks. No exposure-related effects were observed at 5.8 mg/kg/day in the males or 7.3 mg/kg/day in the females. Bilateral aspermatogenesis was significantly increased in the higher dose male groups, indicating that the LOAEL for testicular effects is 29 mg/kg/day. The incidences of bilateral spermatogenesis were 37/64 (58%), 34/50 (64%), 43/55 (78%), 48/65 (74%), and 62/64 (97%), showing a dose-related increase and consistency with a significant reduction in relative testes weight observed at 789 mg/kg/day (59% less than controls). Examinations at week 78 showed aspermatogenesis at 789, but not 147 mg/kg/day (no interim exams were performed in the lower dose groups), suggesting the possibility that the lesion was age- rather than treatment-related at 29 and 147 mg/kg/ day. Also observed in the high dose males was an increased incidence of castration cells in the pituitary gland, which are promoted by reduced testosterone secretions from the testes. Other significant changes were essentially limited to the liver, including increased liver weights accompanied by increased peroxisome proliferation in both sexes at 147 mg/kg/day, spongiosis hepatis in males at 147 mg/kg/day, and hepatocellular neoplasms in males at 147 mg/kg/day and in females at 939 mg/kg/day, but the mechanism for these hepatic effects is probably not relevant to humans (ATSDR, 2002) "Acute, intermediate, and chronic oral exposures to DEHP have profound effects in the rodent liver. Characteristic hepatic effects in rats and mice observed in numerous studies include hypertrophy and hyperplasia, beginning within 24 hours of exposure as reflected by induction of DNA synthesis and mitosis; proliferation of hepatic peroxisomes and, to a lesser extent, mitochondria and lysosomes; induction of peroxisome ß-oxidation enzymes, with an accompanying increase in mitochondrial fatty acid oxidation; decreased cholesterol synthesis and degradation; induction of microsomal CYP4A-associated enzymes; altered concentrations of membrane proteins and lipids; increased production of H_2O_2-degrading enzymes; decreased liver glycogen; alterations in the morphology of the bile ducts; increases in malondialdehyde, conjugated dienes, and lipofuscin deposits, indicating increased cellular concentration of free radical oxygen due to insufficient catalase; possible increased 8-hydroxydeoxy-guanosine in hepatic DNA; and eventual appearance of precancerous altered cell foci, nodules, and tumors. It is generally believed that many of these liver effects are mediated through transcriptional activation of the peroxisome proliferator-activated receptor α (PPARα). The conclusion that the hepatic effects of DEHP are largely due to peroxisome proliferation is supported by findings that increased cell proliferation, hypertrophy, induction of peroxisomal and microsomal fatty acid-oxidizing enzymes, increased fatty acyl CoA oxidase activity, excess production of hydrogen peroxide, decreased plasma lipid levels, and expression and activation of PPARα are common effects among structurally unrelated chemicals and drugs inducing peroxisome proliferation...there are marked species differences in hepatic peroxisome proliferation. In particular, although human liver has low expression of PPARα, the characteristic effects of rodent peroxisome proliferators have not been observed in humans, either in liver biopsies from humans exposed to peroxisome proliferators, or in human hepatocytes exposed to peroxisome proliferators *in vitro*. The overall

evidence indicates that most of the hepatic effects observed in DEHP-exposed rodents, including liver cancer, result from a mechanism that does not operate in humans" (ATSDR, 2002). "A variety of renal changes were observed in all dose groups (e.g., increases in kidney weight, incidence and severity of mineralization of the renal papilla, and severity of normally occurring chronic progressive nephropathy and renal tubule pigmentation), but are unlikely to be toxicologically significant because they appeared to be age-related and/or species-specific. Body weight gain was significantly reduced throughout the study only in the high dose males and females (approximately 15% lower than controls at the end of the study)" (ATSDR, 2002).

"The chronic MRL of 0.06 mg/kg/day was derived by dividing the 5.8 mg/kg/day testicular NOAEL by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)" (ATSDR, 2002). ATSDR does not currently assess cancer potency or perform cancer risk assessments.

The California Office of Environmental Health Hazard Assessment (OEHHA, 1997) has listed DEHP under the health risk category due to carcinogenicity and has a public health goal (PHG) in drinking water at 0.012 mg/L with a primary maximum contaminant level (MCL) of 0.004 mg/L. OEHHA has set a cancer inhalation unit risk for DEHP at 0.0000024 $(\mu g/m3)^{-1}$, with an inhalation slope factor of 0.0084 $(mg/kg\text{-}day)^{-1}$ and an oral slope factor of 0.003 (mg/kg-day) [1]. DEHP is on the Proposition 65 list and has a maximum allowable dose level (MADL) of 410 µg/day for adults, 58 µg/day for infant boys, and 20 µg/day for neonatal boys based on reproductive toxicity by oral exposure utilizing the same David et al., (2000) study that was used by ATSDR.

The NIOSH Recommended Exposure Limit (REL) is 5 mg/m^3 and is also based on the David et al., (2000) study. ATSDR and OEHHA used the David et al., (2000) two-year oral rat study, which indicated that the LOAEL for testicular effects is 29 mg/kg/day, and the NOEL for male rats was at 5.8 (mg/kg/day).

The Texas Commission on Environmental Quality (TCEQ) has listed a short-term effects screening level (ESL) of 50 $\mu g/m^3$ and a long-term ESL of 5 $\mu g/m^3$. TCEQ derived their ESLs for DEHP in 2003 using the occupational exposure limits from NIOSH REL, the TLV from ACGIH, and OSHA PEL of 5 mg/m^3. TCEQ uses the $1/100^{th}$ of the value for the short-term ESL and $1/1000^{th}$ for the long-term ESL (personal communication). Since the MDEQ-AQD derives an ITSL as $1/100^{th}$ of a TLV (with an 8-hour averaging time), it would not be appropriate to use the TCEQ value as they use $1/1000^{th}$ of a TLV when setting a long-term ESL.

ACGIH recommended a TLV-TWA of 4.7 mg/m^3 for DEHP as an occupational exposure limit, assigned an A3 (confirmed animal carcinogen with unknown relevance to humans) notation based on liver tumors reported in rats and mice fed DEHP in their diets. ACGIH discussed several relevant studies from the large number of available animal studies and based their TLV recommendation on the Klimisch et al., (1992) study. Klimisch et al. (1992) performed a 28-day inhalation study of DEHP aerosol in nine-week old Wistar rats. Twenty-seven males (mean weight 226 g) and 17 females (mean weight 226 g) per group per dose were exposed to concentrations of 0, 0.01, 0.05, and 1.0 mg/L (estimated doses of 0, 2.3, 11, and 230 mg/kg/day for males and 0, 3.6, 18, and 360 mg/kg/day for females). All rats were exposed for 6 hours per day, 5 days per week for 4 weeks. "At small concentrations in air (0.015 mg/m^3), DEHP is present as a vapor; however, at high concentrations (300 mg/m^3 and above), it is present as an ultrafine aerosol" (ACGIH, 2001). "At the end of exposure a statistically significant (16%) increase in relative lung weights, accompanied by increased foam-cell proliferation and thickening of the alveolar septi, was found in the males of the highest dose group. Absolute liver

weights were significantly (8.75%) increased in females and relative liver weights were increased in both sexes in the highest dose group, but there were no corresponding histological effects. All these effects were reversed during the 8-wk post-exposure period." The NOAEL of 0.05 mg/L was determined for DEHP. ACGIH used a tenfold uncertainty factor to establish the TLV-TWA of 4.7 mg/m^3.

NTP (2006) conducted an updated review of the scientific literature to determine if there was sufficient evidence to evaluate the reproductive and developmental effects of DEHP. With regard to developmental toxicity, the panel found that, "there is insufficient evidence in humans that DEHP causes developmental toxicity when exposure is prenatal…There is insufficient evidence in humans that DEHP causes developmental toxicity when exposure is during childhood…There is sufficient evidence that DEHP exposure in rats causes developmental toxicity with dietary exposure during gestation and/or early postnatal life at 14-23 mg/kg bw/day as manifested by small or absent male reproductive organs. There were multiple other studies supporting effects on the developing male reproductive tract at higher dose levels. The critical period for effects of the testes extends into the immediate postnatal period with decreased Sertoli cell proliferation seen in male rats exposed by oral gavage to DEHP [at] 100 mg/kg/day on PND 3. There is sufficient evidence that DEHP causes developmental toxicity with 21 days of IV exposure starting at PND 3-5 at 300 mg/kg/day as manifested by decreased testes weight, depletion of germinal epithelium, and decreased seminiferous tubule diameter. The reduced testicular weights persisted through at least 90 days of age. These findings are consistent with those observed after oral exposure" (NTP, 2006).

With regard to reproductive toxicity, the NTP (2006) panel stated that "there is insufficient evidence in humans that DEHP causes male or female reproductive toxicity…There is sufficient evidence in female rats to conclude that DEHP causes reproductive toxicity (decreased numbers of corpora lutea and growing follicles) with dietary exposure at 1088 mg/kg bw/day for multiple generations. There is sufficient evidence in female marmosets to conclude that DEHP causes reproductive toxicity (increased ovary weight and uterine weight) when exposure is by oral gavage at 500 mg/kg bw/day for ~15 months in the peripubertal period...There is sufficient evidence in male rats to conclude that DEHP causes reproductive toxicity when exposure is by oral gavage or in feed at 10-113 mg/kg bw/day for exposures that included gestational and/or peripubertal periods. The critical effects are small reproductive organ size (14-23 mg/kg bw/day), focal tubular atrophy (113 mg/kg bw/day), and Leydig cell hyperplasia and altered reproductive hormones (10 and 100 mg/kg bw/day)…There is sufficient evidence to conclude that DEHP causes reproductive toxicity in adult male mice at dietary exposure levels of 2857 mg/kg bw/day as manifested by decreased testis weight and histopathologic alterations" (NTP, 2006).

DEHP is an endocrine disruptor (Latini et al., 2004; EPA 2007). Endocrine disruptors can display non-monotonic dose responses, wherein effects are seen at very low doses, which are not found at a slightly higher dose, but at much higher doses effects will be seen giving a "U" shaped dose-response curve. DEHP in indoor air is due primarily to volatilization from consumer products and building materials that contain DEHP. In general, concentrations are expected to be higher in indoor air than in outdoor ambient air. Additionally, air concentrations of DEHP in occupational settings (i.e., industrial production) may be significantly higher than general indoor levels.

According to Michigan Department of Environmental Quality Air Pollution Control Rules, an EPA oral RfD can be used to derive an ITSL when an inhalation RfC is not available. The EPA RfD is 0.02 mg/kg/day based on the Carpenter et al. (1953) guinea pig subchronic oral bioassay

LOAEL of 0.04% diet (19 mg/kg bw/day) based on increased relative liver weight which is discussed above. An annual averaging time seems prudent as the Carpenter et al. (1953) study duration was one year. This gives an ITSL at 70 µg/m^3 based on an annual average. The ITSL at 70 µg/m^3 based on an annual average combined with the IRSL of 0.61 µg/m^3 based on an annual average should provide adequate protection for public health.

Available Benchmark Type	Value	Candidate ITSL (µg/m^3)	Candidate ITSL Averaging Time	Candidate ITSL Derivation
DEQ (WRD and RRD) RfD	0.019 mg/kg/day	67	24-Hour	$RfD \times \frac{70\ kg}{20\ m^3/_d}$
EPA RfD	0.02 mg/kg/day	70	24-Hour	$RfD \times \frac{70\ kg}{20\ m^3/_d}$
ATSDR chronic oral MRL	0.06 mg/kg/day	210	24-Hour	$oral\ MRL \times \frac{70\ kg}{20\ m^3/_d}$
OEHHA Maximum Allowable Dose Level (MADL)	20 µg/day	1	24-Hour	$\mu g/_d \div 20\ m^3/_d$
TCEQ Long-term ESL	5 µg/m^3	5	Annual	$ITSL = ESL$
ACGIH TLV-TWA	4.7 mg/m^3	47	8-Hour	$TLV \div 100$
OSHA PEL	5 mg/m^3	50	8-Hour	$PEL \div 100$
NIOSH REL	5 mg/m^3	50	8-Hour	$REL \div 100$

References:

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Appendix A

TERRESTRIAL TOXICITY AND AESTHETICS VALUES

Chemical Name: DEHP CAS No. 117-81-7
Literature Review Date: 11/1/1995
Derived By: D. Bush
Reviewed By: abrock Verification Date: 3/3/14

HNV Tier Status: 1 **WV Tier Status:**
HCV Tier Status: 1

		Drinking Water		Non-Drinking Water
HUMAN HEALTH	HNV	120 ug/L		160 ug/L
	SCREENING LEVEL			
	HCV	14 ug/L		18 ug/L
	POTENCY		0.005745 $(mg/kg/d)^{-1}$	
	HH-BAF-TL.3		184 L/kg	
	HH-BAF-TL.4		534 L/kg	
	RfD (ADE)		0.019 mg/kg/d	
WILDLIFE	WV			
	WV-BAF-TL.3			
	WV-BAF-TL.4			
	RfD			
AESTHETIC	TASTE THRESHOLD			
	ODOR THRESHOLD			

Comments: An error was found in the calculation of the HCV in 1997. In 1997, a male mouse body weight of 0.4 kg (instead of a value of 0.04 kg) was used to derive the species scaling factor. The species scaling factor was corrected and the HCVs were re-calculated. No other changes were made.

HUMAN CANCER VALUE WORKSHEET

Chemical Name: DEHP CAS No. 117-81-7
Developed By: D. Bush 11/12/97; Modified on 1/30/14
Reviewed By: J Bathurst Verification Date: 2/3/14

Key Study: The HCVs for DEHP are based on the incidence of hepatocellular carcinomas/nodules in male B6C3F1 mice (NTP, 1982). The key study and the tumor incidence rate is consistent with the approach used by the USEPA in the IRIS database. However, the slope factor derived below differs from the value provided in the IRIS database primarily because a different species scaling factor was used to generate the R57 value. USEPA raised the mg/kg body weight dose to the 2/3 power to extrapolate from a laboratory animal to humans, whereas, the state's Part 4 Water Quality Standards require raising the mg/kg dose to the 3/4 power. Additionally, EPA notes the use of a default food consumption rate of 13% of the animals' body weight. That default has been updated and the more current value (0.171 kg food/kg BW for male B6C3F1 mice) was used to adjust the daily dose. The following information was entered into the Global 82 model:

Food Concentration (ppm)	Adj. Ave. Dose	Tumors	Animals at Risk
0	0	14	50
3,000	513	25	48
6,000	1,026	29	50

Global 82

$$q = \frac{0.00005435230}{0.017382050892}$$

$q = 0.00088799800$ Species scaling factor = $(70 \text{ kg}/ 0.04 \text{ kg})^{1/4} = 6.47$

$q^* = (q)(\text{species scaling factor})$
$q^* = (0.00088799800)(6.47)$

$q^* = 0.005745$ $(\text{mg/kg/d})^{-1}$

$$RAD = \frac{0.00001}{0.005745} = 0.001740644 \text{ mg/kg/d}$$

$$HCV_{dw} = \frac{(0.001740644 \text{ mg/kg/d})\ (70 \text{ kg})}{2.0 \text{ l/d} + [(.0036 \text{ kg/d} \times 184/\text{kg}) + (.0114 \text{ kg/d} \times 534 \text{ l/kg})]} = \textbf{14 ug/l}$$

$$HCV_{non\text{-}dw} = \frac{(0.001740644 \text{ mg/kg/d})\ (70 \text{ kg})}{0.01 \text{ l/d} + [(.0036 \text{ kg/d} \times 184 \text{ l/kg}) + (.0114 \text{ kg/d} \times 534 \text{ l/kg})]} = \textbf{18 ug/l}$$