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Reference Dose and Reference Concentration Rounding in IRIS: Risk Assessment Ramifications

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Abstract

Commonly, reference doses and reference concentrations, toxicity factors supporting non-cancer assessments for the chemical exposures of humans, are rounded values. While the U.S. EPA's Integrated Risk Information System rather evidently employs this rounding practice so as to arrive at toxicity values that are uniform and simple in appearance, the particulars of the rounding approach are only loosely discussed. The analysis provided here found that reference dose and reference concentration rounding, occurring respectively, for some 50% and 87% of chemicals of methodically developed lists, is a fully indiscriminate and highly inconsistent process. Toxicity factors being either rounded up or down are close to equiprobable events. Further, through rounding, sizeable percentages (e.g., ca. 20%) of the toxicity factors bear magnitude increases or decreases of 20% or more, and an overall absolute shifted magnitude figure (i.e., for both reference doses and reference concentrations, and independent of rounding direction) was approximately 12%. The consequences of seemingly unnecessary rounding for hundreds of chemicals, in terms of the non-cancer/hazard outcomes of risk assessments, are reviewed.

Introduction

En route to establishing reference doses (RfDs) and reference concentrations (RfCs) in support of non-cancer assessments, such as those conducted for hazardous waste sites, the results of hopeful and directed toxicity testing with laboratory animals are cautiously scrutinized. Although the benchmark dose (BMD) methodology [1] has come to play an increasing role in setting RfDs and RfCs via the use of a mathematical dose-response model, most RfDs and RfCs are derived through establishing No Observed Adverse Effect Levels (NOAELs), [2,3] a central concern of this paper. Procedurally for a given chemical, a considerable volume of peer-reviewed reports and articles is first examined, leading to the designation of a critical study. It is from the critical study that the NOAEL, the highest experimental dose for which no adverse health effects have been documented, is identified. Assumed to be safe, a series of uncertainty factors (UFs) and a modifying factor (MF) are nevertheless applied to NOAELs, to arrive at RfDs and RfCs. Uncertainty factors (UFs), generally 10-fold factors, reduce the magnitude of the NOAEL in an effort to offset the influences of such phenomena as animal-to-human extrapolation, subchronic exposure-to-chronic exposure extrapolation, and datasets being deemed incomplete. The MF, with a value ranging from greater than zero to a maximum of 10, is applied using professional judgment.

Quite evidently, pursuant to UF and MF application, RfDs and RfCs are rounded prior to use, rendering them into their final forms. Thus the EPA's Integrated Risk Information System, [4] in addition to identifying a chemical's critical study, NOAEL, and the pertinent UFs and MF applied, will also display RfDs and RfCs that, in nearly every case, have been adjusted somewhat in their decimal places. This generally is in keeping with approaches adopted across the sciences; commonly *bona fide* rules exist for rounding to significant figures [5,6] or to n decimal places. U.S. EPA practice, as stated in its seminal human health risk assessment (HHRA) guidance document (USEPA 1989) [2] is to express oral RfDs (RfD_os) as one significant figure (in units of mg/kg-day). It is noteworthy that this same guidance does not identify a rounding rule for inhalation reference concentrations (RfC_is), one of two toxicity factors explored in this paper. It is also noteworthy that this guidance

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does not recognize that the applied one significant figure rule might come at a cost in terms of sacrificed accuracy for resultant hazard estimates. Thus, the degree of increase or decrease in RfDs and RfCs, attributable to the commonplace rounding, is never discussed despite the rounding often translating into magnitude shifts of 20 or 30%. As an example, butyl benzyl phthalate's oral RfD prior to rounding is 1.59E-01. After rounding though, it is 2.00E-01, a figure 27.9% larger. This paper is a methodical review of the rounding of IRIS-available RfDs and RfCs used respectively, in the calculation of non-cancer hazard for the ingestion and inhalation exposure pathways. The findings are then considered in a discussion of the ramifications of routinely applied rounding on non-cancer assessment efficacy.

Methods

The EPA's 2019 Regional Screening Level (RSL) table [7] served as the initial source of chemicals for the study. RfD_o and RfC_i universes to be subjected to the rounding analysis were developed following the scheme of Tannenbaum and Comaty [8] excluding from consideration, chemicals with toxicity factor development features that could serve to confound findings, or that had issues outstanding (e.g., having an archived or withdrawn status). As a first implemented measure to ensure an equitable review of toxicity factor rounding, chemicals with a lower position in the preferred peer review hierarchy for toxicity values to be used in human health risk assessment (HHRA; i.e., other than IRIS; USEPA 2003) [9] were excluded. RfD_os and RfC_is that had been set using the BMD methodology were also removed, given the critical study-specific nature of the analysis (i.e., the focus on rounding that occurs for individual studies as opposed to rounding done for an amalgam of studies; Tannenbaum and Comaty) [8].

For the retained chemical lists, the principal analysis extended to identifying those chemicals with a rounded toxicity factor, determining the percentage of these that were either rounded up or rounded down, and expressing the range of the degree

to which RfD_os and RfC_is had been increased or decreased through rounding. Rounding inconsistency was evaluated in three ways. First, the frequency and directionality of rounding was examined for what are hereafter termed 'mathematical' RfD_os and RfC_is (i.e., the quotients resulting from the division of study NOAELs by their respective UFs) whose last decimal, either in the tenths or hundredths place, was 5 (i.e., a mid-point value). Second, several paired or grouped chemicals were selected from the RfD_o study universe to illustrate curiosities with regard to mathematical RfD_os being rounded or not prior to their placement on the RSL table. Finally, a series of hypothetical soil concentrations were carried through a standard human health chemical exposure pathway (the incidental soil ingestion of a site resident) to highlight the corrupting influence of applied RfD_o and RfC_i rounding when a technical basis in support of such is lacking.

Results

As Table 1 illustrates, substantial percentages of RSL Table chemicals with RfD_os and RfC_is derived from laboratory animal studies, were screened out of the rounding analysis. A lower position in the peer-review hierarchy (i.e., secondary to IRIS as the review source) accounted for the greatest percentage of chemicals being excluded from consideration. Pursuant to chemicals being eliminated for a number of reasons, 37 and 20% respectively, of the initial RfD_o and RfC_i universes were retained for study. Continuing with the rounding analysis, fully half of the RfD_os evidenced rounding, while 87% of the RfC_i universe had this feature (Table 2). This dichotomy was observed to reflect the relative percentages of mathematical RfD_os and RfC_is that either did or did not divide evenly. To illustrate, fortuitously, only 13% of mathematical RfC_is retained for analysis had whole integers preceding the exponent, a situation that obviates the need for rounded or simplified toxicity expressions. In contrast to this difference between the universes, the partitioning of RfD_os and RfC_is into those with rounding up and those with rounding

Table 1: Establishing the RfDs and RfCs submitting to the rounding analysis.

Basis for elimination	Number of chemicals removed from an initial 2019 RSL Table universe of 660 oral RfDs	Number of chemicals removed from an initial 2019 RSL Table universe of 232 inhalation RfCs
Lower position in peer-review hierarchy	309	141
Benchmark dose methodology used	44	26
Lacking adverse effect	5	0
Human as test subject	15	8
Non-mammal test subject	2	0
Other[1]	40	11
Sum of chemicals removed	415	186
Chemicals retained for analysis	245	46

[1]Includes designations such as 'archived', 'not evaluated', 'not available at this time', and 'withdrawn'.

Table 2: Rounding analysis summary statistics for the chemical universe considered.

	RfD_o	RfC_i
Number of chemicals with a rounded toxicity factor	124	40
	(50.6% of universe)	(87% of universe)
% of 'rounded up' toxicity factors	58.1	55.0
% of 'rounded down' toxicity factors	41.9	45.0
Magnitude range of 'rounded up' toxicity factors	0.55% - 33.3%	2.04% - 25.0%
Arithmetic mean of the degree of toxicity factor rounding (absolute values considered)	13.3%	12.1%
Magnitude range of 'rounded down' toxicity factors	3.61% - 30.07%	3.03% - 31.03%
Arithmetic mean of the degree of toxicity factor rounding (absolute values considered)	11.4%	11.7%

Table 3: Rounding inconsistency analysis for mathematical RfD_os and RfC_is with 5 as a last decimal figure.

Mathematical RfD_o decimal value considered	RfD_o				
	number of chemicals without rounding	number of chemicals rounded up	(Absolute) arithmetic rounding mean (%)	number of chemicals rounded down	(Absolute) arithmetic rounding mean (%)
X.5 (e.g., 0.5)	25	19	19.63	1	14.29
X.X5 (e.g., 2.15)	0	8	3.57	5	10.70
Mathematical RfC_i decimal value considered	RfC_i				
	number of chemicals without rounding	number of chemicals rounded up	(Absolute) arithmetic rounding mean (%)	number of chemicals rounded down	(Absolute) arithmetic rounding mean (%)
X.5 (e.g., 0.5)	0	4	10.51	0	---
X.X5 (e.g., 2.15)	0	0	---	0	---

down, was nearly even. Table 2 also shows that the similarity in the degree of rounding (i.e., how much RfD_os and RfD_is were increased or decreased through rounding) was also strikingly similar for the two toxicity factors, this when expressed both as a range, and as an absolute mean (i.e., independent of rounding direction) of the values for each universe. The absolute magnitude of rounding across all considered cases (i.e., for RfD_os and RfC_is, and for rounded up and rounded down values) straddled a figure of 12%.

Table 3 reports the results of a first foray into quantifying rounding inconsistency for RSL Table RfD_os and RfC_is. While the RfC_i universe was too small to demonstrate irregularities with regard to how values that terminate with a 5 in the decimal portion of a toxicity factor are rounded (i.e., in which direction to round, if such is done at all), the RfD_o statistics are dramatic. When a 5 is in the tenths decimal place, instances are rather evenly split between values that are rounded and those that are not (i.e., there are 20 rounded values within a universe of 45). The ratio of rounded up to rounded down values however, is quite lopsided; of the 20 rounded

values, only one is rounded down.

Notable occurrences of rounding inconsistency with RfD_os are profiled in Table 4. Aside from the examples highlighting inconsistency with regard to rounding direction, the tabularized information incorporates concerns over unnaturally boosted or reduced RfD_os, particularly where RfD_o magnitude was shifted by 20% or more. The examples support the overall observation that IRIS RfD_o and RfC_i rounding (following from application of the one significant figure rule) follows no pattern whatsoever (see Discussion).

Critical RfD_o rounding manifestations of underplayed and exaggerated hazard outcomes are evaluated in Table 5. The first three rows profile chemicals whose RfD_os were 'rounded up', recalling that the larger the RfD_o, (as the denominator of the hazard quotient [HQ] construct), the smaller a resultant HQ will be. The selected hypothetical chemical concentrations in these rows correspond to HQs that are at unity (a value of 1.0) for a modeled site resident where the RSL Table (rounded) RfD_o is used. Corresponding HQs for each of the chemicals where the mathematical RfD_os were

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Table 4: Emblematic RfDo rounding inconsistencies in IRIS/the RSL Table.

Chemical	Mathematical RfD_o	RSL Table RfD_o	Analysis
bromomethane	1.40E-03	1.40E-03	Bromomethane and furan, with identical mathematical RfD_os, should have identical RfD_os appearing on the RSL Table as well. Instead, bromomethane was not rounded, and furan was rounded down (by just over some 28%).
furan	1.40E-03	1.00E-03	
benzaldehyde	1.43E-01	1.00E-03	Benzaldehyde's mathematical RfD_o (i.e., the digits, and discounting the exponent) is slightly higher than that of bromomethane. While bromomethane's RfD_o is not rounded, benzaldehyde's is rounded, and significantly so (reduced by 30%).
fenamiphos	2.50E-04	2.50E-04	Hexachlorophene's mathematical RfD_o, identical to that for fenamiphos, is rounded up by 20% while fenamiphos's mathematical RfD_o is not adjusted.
hexachlorophene	2.50E-04	3.00E-04	
methyl methacrylate	1.36E00	1.40E00	We would expect methyl methacrylate's mathematical RfD_o to be rounded in some way since its last (i.e., hundredths place) digit is not a 0 or a 5, and given that benzaldehyde (in this table's first example) is so handled on the RSL Table. It is curious that trichlorobenzene 1,2,4-, a chemical with a non-zero hundredths place value (i.e., before the exponent) that is larger than methyl methacrylate's hundredths place value (i.e., 8 vs. 6), and with the entire value being so close to 1.5, is rounded down to 1.00 (E-02), and not to 1.40 as occurs with benzaldehyde (above). Of note, trichlorobenzene 1,2,4-'s RfD_o reduction through rounding, of 32.43%, is the greatest magnitude adjustment of any RSL Table RfD_o.
trichlorobenzene, 1,2,4-	1.48E-02	1.00E-02	
malation	2.30E-02	2.00E-02	The RSL Table contains numerous instances of mathematical RfD_os and RfC_is with decimals of 0.30 or 0.40 being rounded (either up or down), as occurs here with malathion. While their exponents are different (something that this paper's analysis did not show to be a factor in rounding direction), malathion and acrylic acid are very differently treated, with malathion's actual (i.e., RSL Table) RfD_o having been reduced just over 13% and acrylic acid's RfD_o being left unchanged.
acrylic acid	5.30E-01	5.30E-01	

Table 5: Risk assessment outcome manifestations due to inconsistent toxicity factor rounding.

Soil chemical	Hypothetical exposure point concentration (mg/kg)	Incidental soil ingestion hazards (HQs) for a hypothetical site resident[1]			
		Mathematical RfD_o	HQ	'Rounded Up' RSL Table RfD_o	HQ
endrin	25	2.50E-04	1.20	3.00E-04	1.00
hexabromodiphenyl ether	17	1.50E-04	1.36	2.00E-04	0.93
octabromodiphenyl ether	250	2.51E-03	1.20	3.00E-03	1.00
Soil chemical	Hypothetical exposure point concentration (mg/kg)	Mathematical RfD_o	HQ	'Rounded Down' RSL Table RfD_o	HQ
chloroform	1000	1.29E-02	0.93	1.00E-02	1.21
furan	100	1.40E-03	0.86	1.00E-03	1.20
trichlorobenzene, 1,2,4-	1000	1.48E-02	0.81	1.00E-02	1.20

[1]Computed HQs do not follow straightly from the toxicity information of the 2019 RSL Table. That RSL Table bears numerous erroneous risk-based concentrations (rbc), as in those for the incidental soil ingestion uptake route of residents and industrial workers. The erroneous values reflect standard exposure factors (e.g., adult body weight; exposure duration [in years]) adopted several years ago (USEPA 2014), not having been implemented in the rbc calculations.

Table 6: Rounding magnitude summary: Percentages of rounded RfDo and RfCi universes with noteworthy magnitude increases or decreases.

Toxicity factor	RfD and RfC rounding manifestation		
	Toxicity factor increased or decreased by 10% or more	Toxicity factor increased or decreased by 20% or more	Toxicity factor increased or decreased by 30% or more
RfD_o	51.6	21.8	5.6
RfC_i	47.5	17.5	2.5

used, are observed to be unacceptable in risk assessment terms, with values approximating 1.2. The lower three table rows profile chemicals with 'rounded down' RfD_os. These lesser magnitude toxicity factors in the HQ construct's denominator give rise to relatively enlarged HQs (again, at a value of approximately 1.2). When the mathematical RfD_o is used for these chemicals, the selected soil concentrations lead to HQs that are acceptable/safe, with values ranging from 0.81 to 0.93. Buttressing these observations is the reporting of Table 6, a quantification of the frequencies with which RfD_os and RfC_is are, through rounding, increased or decreased by noteworthy degrees (i.e., 10-30%).

Discussion

In the hard sciences, only a small handful of reasons account for the phenomenon of rounding numerical values. Rounding to a fixed number of significant figures or to *n* decimal places may first be done for convenience, allowing for an easier way to express, reference, or manipulate values in certain instances. By way of example, it is less clumsy to say that there are 1.7 items in a measure (e.g., insects on an average plant leaf) than it is to say there are 1.739 items in a measure. A second reason for rounding is so as to have all the numerical values within a given set bear notable consistency. Seemingly as a third reason, the intent with number rounding is to confer a respectable degree of accuracy on numerical values to be used (i.e., to enable working with values that better approximate the real-world condition). One last reason for rounding numbers is so as to be compliant with a standard that science has recognizably adopted. With regard to the present study and its focus on the degrees of rounding of RfD_os and RfC_is reported in IRIS and the RSL Table, these four bases for rounding do not appear to be relevant, or to have been implemented, as discussed below. Further, the case can be made that without a scientifically sound (as opposed to a programmatic) rationale for rounding RfD_os and RfD_is provided, and with the great rounding inconsistency observed for these toxicity factors, rounding has undoubtedly been detrimental to non-cancer assessment, allowing erroneous and misleading HQs to form.

Arguably, there is no convenience supplied to non-cancer assessment with the rounding or truncating of computed toxicity factors evident in RSL Table RfD_os and RfC_is. Calculated RfD_os and RfC_is are almost never manipulated by hand in risk assessment work; they are rather drawn from existing electronic databases,

and incorporated into equations on the desktop as part of a highly automated process that generates hazard outcomes and related computations. Neither a risk assessor or a computer therefore, works any harder to number crunch toxicity factors of two or three decimal places or of multiple significant figures, than they do when manipulating toxicity factors that are rounded to a nearest (whole) integer (e.g., 3.00E-03). It is possible nevertheless, that ongoing and routinely implemented RfD_o and RfC_i rounding reflects the thinking that such action simplifies the tasks of risk assessors. An irony is that while not supplying any such convenience for the greater risk assessment process, RfD_o and RfC_i rounding necessarily supplies notable inconsistency and introduces the possibility of inaccurate outcomes (addressed further into this Discussion).

Empirically, the greatest degree of consistency in RfD_o and RfC_i generation is attained when there is straightforward division of each chemical-specific NOAEL by its respective (cumulative) UF. This is because a NOAEL (the HQ's numerator) depicts an actual study dose that was used, and that by definition is a study's highest dose that did not produce a toxicological response, adverse or otherwise [2,8]. Regardless of its form, it is perfectly appropriate to work with RfD_os and RfC_is that form from the division of true study NOAELs by commonplace UFs such as 1,000 or 3,000. Examples would be aluminum phosphide with a NOAEL of 0.043 mg/kg/day, and acetophenone with a NOAEL of 423 mg/kg/day. While it may be unfortunate that UFs regularly assume three order-of-magnitude and greater values, and transparently appear each time as unimaginative products of a series of ten-fold factors, there is no need for any further adjustment of the quotients produced (i.e., the RfD_os and RfC_is). Most critical to this study and its examination of rounding, is that NOAELs that are 'cleanly divided' by UFs (i.e., that present as figures with either no decimal preceding the exponent, or often enough, with a decimal of 0.5; Table 2) are no more accurate than NOAELs that do not divide this way. A practical example demonstrates this.

The ingestion route NOAEL for the chemical, glycidaldehyde is 1.09 mg/kg/day. This dose failed to elicit a toxicological response in chronically exposed rats, whereas the test dose immediately above it, of 2.23 mg/kg/day, triggered enlarged adrenal glands, hydropic re-

nal pelvis, and several other sublethal effects in the test animals. Procedurally, dividing the NOAEL by the critical study's cumulative UF of 3000, gives rise to the RfD_o of 3.63E-04. Importantly with regard to this simple mathematical construct, there is no reason to be suspect of this RfD_o's magnitude, as in feeling that it should either be reduced or enlarged. The rounding up though, of the 3.63E-04 mg/kg/day figure (by 10.19%) to the 4.00E-04 mg/kg/day figure displayed in IRIS and the RSL Table, a happenstance of abiding by the well-intended practice of rounding to one significant figure, has nevertheless acted to lessen glycidaldehyde's toxicity (i.e., potency). A 'rounded up' glycidaldehyde RfD_o as the divisor for a receptor's computed intake (perhaps that for an outdoor worker under the incidental soil ingestion pathway), will necessarily give rise to HQs that are 10.19% lower than should be. Potentially, glycidaldehyde HQs produced with the RSL Table-available 'rounded up' RfD_o are masking what would otherwise be unacceptable hazards (see Table 5). Transparently however, IRIS is not attentive to this reality; some 50% and 87% of considered RfD_os and RfC_is respectively, have been rounded solely because their quotients did not cleanly divide, i.e., because the emerging quotients did not present as values with one significant figure. In effect, chemicals whose mathematical RfD_os and RfC_is are not of one significant figure are being penalized with regard to having their truer potencies expressed. Further, the subject analysis identifies an unstated but nevertheless apparent IRIS objective, namely to have all RfD_os and RfC_is assume a uniform appearance, with whole integers preceding an exponent. It is precisely the attention given to this objective that is responsible for compromised accuracy, as explained below.

The perception might be that the dominant factor compromising the accuracy of RfD_os and RfC_is (and increasing HQ uncertainty) is that of whole integer values being left as they are, while all other mathematical RfD_os and RfC_is are rounded. While such does constitute a source of inaccuracy, the case can be made that the dominant factor compromising non-cancer assessment accuracy is the recurrent inconsistency in rounding direction (Table 3 and Table 4). We could, theoretically, imagine USEPA toxicologists and IRIS managers adopting a position or policy (without supportive evidence) that through their derivation, mathematical RfD_os and RfC_is commonly emerge slightly attenuated. In that case, it might be decided that all mathematical RfD_os and RfC_is, independent of any fractional values (i.e., decimals) they may bear, should be adjusted upwards by a fixed degree (perhaps 4%). Since advanced toxicological study never proceeds in efforts to determine if/that chemical-specific mathematical RfD_os and RfC_is are in fact, attenuated/underestimated (or overestimated), it becomes clear that values are not rounded for the sake of supplying greater accuracy.

A widely held practice in science and engineering is rounding to a fixed number of significant figures, a more general-purpose technique than rounding to *n* decimal places, since it handles numbers of different scales in a uniform way. By way of example, a city's population might only be known to the nearest thousand and reported as such (e.g., 52,000), while a country's population might only be known to the nearest million, and expressed that way (e.g., as 52,000,000). The city population might be in error by hundreds, and the country population by hundreds of thousands, but there is an equity in such reporting. Both populations have two significant figures, with this reflecting the significance of the error being the same for both, relative to the size of the quantity being measured. We should expect the number of significant figures of toxicity study NOAELs to be maintained through all subsequent usages, as in computed mathematical RfD_os and RfC_is, and then, final-form RfD_os and RfC_is as found on the RSL Table. This paper's review however, observed that the only instances of a maintained number of significant figures were for that specific case where serendipitously, study NOAELs were of one significant figure (e.g., 0.04 mg/kg/day; 2.00 mg/kg/day). Thus, a constancy in the number of significant figures was observed only some 28% and 5% of the time for RfD_os and RFC_is, respectively. As an example, bromodichloromethane's NOAEL and mathematical RfD_o, respectively, were each of three significant figures, at 17.9 (mg/kg/day) and 1.79E-02, while this chemical's RSL Table-available RfD_o of 2.00E-02, reflecting an unintended 11.73% toxicity decrease, has but one significant figure. The pivotal point to secure here is that whether the mainstay practice of rounding IRIS RfD_os and RfC_is to one significant figure occurs so as to offset imprecision associated with application of four and five-digit UFs or for some other reason, the practice comes at a cost. The rounding, appearing to be centered more on a formatting concern, is necessarily compromising expressions of toxicity and thereby, accuracy.

The frequency of occurrence statistics for RfD_os and RfC_is that have been increased or decreased by 20% or more as a consequence of IRIS rounding (Table 6), may not at first blush, seem problematic for risk assessments. A consideration of the magnitudes that HQs regularly assume in US risk assessments though, dispels such thinking. An exhaustive review of a near decade's worth of Superfund Records of Decision (ROD) and ROD amendments, found that the largest category of unacceptable hazard indices (HIs), at approximately 27%, were those with magnitudes ranging from just above 1.0 to 10 (a situation notably different from what occurs regularly in ecological risk assessments; Tannenbaum, et al. 2003) [10]. What practitioners then, might term only slight HQ increases or decreases (e.g., 1.0 to 1.2, or 1.2 to 1.0) attributable to unnecessary rounding up or down (i.e., where a technical basis for rounding is lacking), could be providing a basis for improperly drawn conclusions. Thus, with IRIS's routinely implemented

one significant figure rounding (that often enough obscures a significant degree of RfD_o and RfC_i specificity), HQs or HIs slightly above unity may not mean that a human receptor's exposure is unhealthful, or that site remedial action should proceed. Such might only be the effect of an RfD_o or RfC_i having been unnecessarily rounded down. Similarly, RfD_os and RfC_is that have been fortuitously increased through rounding to give rise to HQs and HIs slightly below unity, might be masking instances that in actuality, very much need to be addressed. In the discussion here it is critical to note that in human health non-cancer assessment a HQ value of 1.0 is not scientifically, a bright line. While regulators may well understand this and thereby not insist that a HQ of 1.2 is unacceptable, the 'slight (magnitude) HQ increases' mentioned above, when presented in a somewhat different light, can easily be interpreted by regulators and other stakeholders as problematic. Thus, for a rounding-caused HQ shift from 1.2 to 1.4 (i.e., a shift of the same magnitude when climbing from 1.0 to 1.2), many a regulator and stakeholder could be expected to flag the (higher) outcome as firmly unacceptable.

Pursuant to what the subject analysis has revealed, the perception might be that the inaccuracies and other difficulties engendered with the indiscriminate rounding of RfD_os and RfC_is, can be avoided through engineering toxicity studies to always result in NOAELs that are always of whole integers (e.g., 3.00E-04). For two reasons however, such is not a viable option. First, as a simple consequence of human endeavor, researchers commonly do not arrive at the precise (and presumably) numerically even chemical doses (e.g., 80 mg/kg) they intend to administer to their animal subjects. Also, at the outset of a dosing study, one cannot know what the study's actual UFs and MF will be. A realistic view is that whole integer RfD_os and RfC_is will not be generated on every occasion.

It is the author's position that IRIS-sanctioned rounding of RfD_os and RfC_is is not inconsequential for HHRA. While the long-time indoctrinated chronic RfD definition recognizes the variability that this toxicity value can assume (i.e., with these estimates having uncertainty spanning perhaps an order of magnitude or greater; USEPA 1989) [2], such variability need not arise from an inconsistently applied value adjustment process. While adhering to significant figure rounding is a standard practice across many sciences, its application in the case of RfD_os and RfC_is may be a detrimental one. Toxicity value specificity is clearly being undermined at the expense of values being crafted with a shortened/simplified appearance. Further,

recognition of the frequent cases of inconsistently applied rounding in fashioning these toxicity factors should suggest that the significant figure rounding be withheld. A final example concretizes this argument. Chloroform's critical study (converted) lowest observed adverse effect level (i.e., the toxicological basis of the chemical's RfD_o) is a 12.9 mg/kg/day. After applying the UF of 1000, the final RfD_o becomes 1.29E-02 mg/kg/day. This value could be used as is, with no bias being supplied in any HQ computations that may follow. Its adjustment though, to a value of 1.00E-02, a figure over 22% smaller, will necessarily impart bias to subsequent HQs produced. Dispensing with the rounding of RfD_os and RfC_is, ordinarily applied with the intent only of adhering to a standard often seen in the sciences, would allow for more truthful hazard estimates to occur.

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Statement of Equal Authors' Contribution

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