

THE ESTIMATION OF PROPERTIES EMPLOYED TO PREDICT THE ENVIRONMENTAL FATE AND TRANSPORT OF HYDRAZINE-ALTERNATIVE HYPERGOLS

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ABSTRACT

Under a program to design and develop hydrazine-alternative hypergols, assessments of the risks candidates pose to human health and the environment are to be made and considered along with traditional engine performance criteria throughout the selection and development process. Seeking to base assessments for the earliest stages of the process on quantitative structure property relationships (QSPRs), published QSPRs for 6 physical properties commonly employed as input for fate, transport and effect modeling were identified and evaluated. The evaluation focused on the reliability of the identified QSPRs' estimates for the two classes of compounds considered to have the best prospects for replacing hydrazine-based hypergols: saturated, tertiary multiamines (STMs) and ethanamine azides (EAs). The study indicates that QSPRs contained in a program provided by the US Environmental Protection Agency yield reasonable estimates for STM normal boiling points, (ambient) vapor pressures, octanol-water partition coefficients, water solubilities and air-water partition coefficients. The program's estimates for EAs, on the other hand, proved poor or there was insufficient data with which to validate them. Alternate methods for estimating EA normal boiling points and vapor pressures are recommended. Gaps that remain in the desired protocol are identified, and approaches to filling them are proposed.

1. INTRODUCTION

The US Army is pursuing the development of the Impinging Stream Vortex Engine (ISVE) for tactical missile applications (Michaels and Wilson, 1995; Nusca and McQuaid, 2005). The ISVE is a hypergolic propulsion system concept, i.e., one that employs a liquid (or gel) bipropellant combination that ignites spontaneously upon mixing at low temperatures and pressures. Hypergolic propulsion systems have many potential advantages over the solid propellant-based rocket motors currently employed to propel tactical missiles. Among them is active thrust control, which, increasing targeting options and range, will increase a tactical missile's lethality while reducing the vulnerability of its launch platform. Because the fuel and oxidizer are stored separately in hypergolic propulsion

systems, they are also inherently insensitive to a variety of stimuli that can produce catastrophic events in solid-propellant-fueled rocket motors. The space required for traditional hypergolic systems, however, prevents them from being integrated into airframes as small as those of tactical missiles. The ISVE concept, which facilitates the design of more compact engines, appears capable of changing this paradigm.

Of the many factors that (will) influence the size of the ISVE, two of the most important are performance-related attributes of the fuel/oxidizer combination—namely, ignition delay and density specific impulse ($\rho \cdot I_{sp}$) (Clark, 1972). Coupled with other considerations such as the temperature ranges of the fuel and oxidizer as liquids, the fuel/oxidizer combination with the best combination of ignition delay and $\rho \cdot I_{sp}$ is monomethylhydrazine/inhibited red fuming nitric acid (MMH/IRFNA). Unfortunately, MMH is acutely toxic and a suspected carcinogen (Schmidt, 2001). As such, it would create a logistics burden and a threat to the sustainability of Army training ranges. Therefore, MMH is not considered a viable option, and finding a suitable alternative is necessary for the benefits of hypergolic propulsion to be realized in tactical missiles.

Searching for an alternative to MMH, the Army Aviation and Missile Research Development and Engineering Center (AMRDEC) and the Army Research Laboratory (ARL) have studied and tested a variety of compounds (McQuaid, M. J., 2002; McQuaid, et al., 2002; McQuaid, et al., 2005; McQuaid, 2006). All fall short of MMH, but their work suggests that a saturated, tertiary multiamine (STM) or ethanamine azides (EA) will prove to be suitable. STMs are compounds whose molecules have more than one amine N-atom ($>N-$), those N-atoms are bonded to methyl ($-CH_3$) and methylene ($-CH_2-$) groups (only), and their molecules have no multiple order bonds. Ethanamine azides (EAs) are compounds whose molecules have at least one azide group ($-N=N=N$) and one amine N-atom, and the azide group and the amine N-atom are separated by an ethylene chain. An example of an STM (TMEDA) and an EA (DMAZ) is shown in Figure 1. TMEDA is an acronym for Tetramethyl-ethylene-1,2-diamine. It has the more formal name 1,2-Bis(dimethylamino)ethane. DMAZ is more formally named 2-Azido-N,N-dimethylethanamine.

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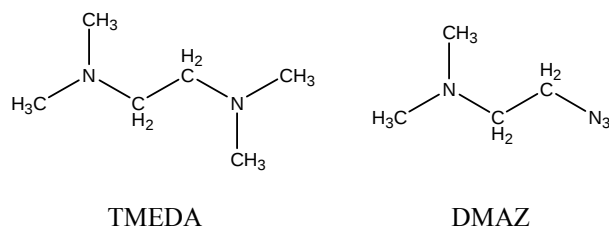


Figure 1. A representative STM (TMEDA) and EA (DMAZ).

Beyond predicting or demonstrating the performance potential of STM and EA candidates, AMRDEC and ARL have given some consideration to other issues such as their cost and potential risk to human health (based on general expectations for the toxicity of certain chemical functional groups) (McQuaid, 2006). But other considerations are germane to the selection process. For example, though risks to human health are the most notable drawback to MMH (and other hydrazine derivatives), and indications are that STMs and EAs are less harmful to humans than MMH, their potential impact on other organisms can not necessarily be inferred from knowledge of their toxicity to humans and needs to be assessed. In addition, a compound's transport and fate in the environment will be relevant to determining the ramifications of releases – both accidental and intentional. Since such factors have the potential to scuttle a candidate, the chance that time and money will be wasted developing candidates that will later prove to pose unacceptable risks to human health or the environment exists. To reduce that chance, ARL is collaborating with the US Army Center for Health Protection and Preventive Medicine (CHPPM) to develop an environmental risk assessment protocol that can be used to inform the selection process throughout the development cycle.

Among the inputs CHPPM identified as being needed to assess a candidate's risk to human health and the environment are values for 6 properties used to model a compound's transport and fate. Those 6 properties are: normal boiling point (*NBP*), vapor pressure (*VP*), water solubility (*WS*), octanol-water-partition coefficient (*K_{ow}*), air-water partition coefficient [which is also referred to as Henry's Law constant (*HLC*)], and affinity for organic carbon (*K_{oc}*). An issue, however, is the means of acquiring such data during for the earliest stage of the development process. During this stage : (1) the number candidates, some of which may not be commercially available, (2) the range of fate- and transport-relevant properties that need to be considered, and (3) the cost to determine those properties experimentally, dictates that they be estimated via computationally based methods. Quantitative structure property relationships (QSPRs) offer one means of obtaining the estimates, but their

empirical nature invariably raises questions about the credence to give them. This paper considers this issue.

Towards identifying "reliable" QSPRs for estimating the 6 properties of interest, models provided by the Environmental Protection Agency were evaluated. Bundled in a Windows® based package called EPI (Estimation Program Interface) Suite™, they are publicly available and free. The only input needed is a Simplified Molecular Input Line Entry System (SMILES) representation for the molecular structure of the compound of interest. Since the package's QSPRs are easy to use and had the potential to avoid the need to develop QSPRs from scratch, they were considered highly attractive candidates for estimating the desired property data. The evaluation identifies property/compound class combinations for which reliable QSPRs were found and identifies those for which QSPRs remain to validated or developed.

2. VALIDATION CONSIDERATIONS

All of the EPI-Suite QSPRs evaluated in this paper can be described as bond or group additivity models. That is, the "structures"—i.e., the S in QSPR—are heuristically defined bonds or groups of atoms into which a molecule may be divided. Group definitions are typically based on (1) the atoms to which a group's "core" (atom) is bonded and (2) the "order" of those bonds. Bond order definitions; i.e., single (-), double (=), triple (≡), or resonant, typically follow from valence electron schema. Coefficients for each group are obtained from a parameterization of the model to data for a training set of compounds whose molecules can be defined in terms of the groups in the model. Estimates for a compound are obtained by assigning (all) its structures to groups (or bonds) defined in the model, and summing the corresponding coefficients. Unless a compound can be completely "built" from the groups (or bonds) defined in an additivity (QSPR) model, the model's estimate for the compound can not be considered reliable. Cases where this occurs are noted below.

Assuming that a compound can be completely built from the groups (or bonds) of an additivity (QSPR) model, various criteria have been proposed as bases for considering a model "reliable." Hulzebos et al. suggest that each group in the model needs to be found in at least 4 compounds in the training set, and that the *R*² value for the model's fit to the training set data exceed 0.7 (Hulzebos et al., 2005). Aptula et al., on the other hand, consider *R*² to be a poor criterion upon which to base expectations for a model's predictive capability (Aptula et al., 2005). They suggest that the root mean square error (*RMSE*) for a test set:

$$RMSE = \sqrt{\frac{\sum_i (Y_i^{pred} - Y_i^{exp})^2}{N}}$$

where Y is the value of experimentally measured property and N is the total number of compounds (i) in the set, is a better basis.

The author attempted to consider all three criteria, but only R^2 values are readily gleaned from the reference material that the EPI-Suite program provides. (All the QSPRs evaluated had R^2 values greater than 0.7.) For the other two questions, the answers are not obvious. All the QSPRs that were evaluated were derived from training sets and validated with test sets that contained measured values for from hundreds to thousands of compounds. But details such as the total number of different groups in the model and the number of compounds in the training set having the groups of interest were difficult to extract from the reference material.

To address these issues, where possible, validation sets were constructed from literature searches. Sources searched included the NIST Chemistry WebBook (webbook.nist.gov/chemistry/) Chemnetbase (www.chemnetbase.com), and the Sigma-Aldrich web site (www.sigmaaldrich.com). For azides, the data found from these sources were supplemented with data provided by AMRDEC and a paper published by Lee et al. (Lee et al., 1989). Searches of the electronic databases were typically conducted by specifying stoichiometries ($C_xH_yN_z$) for a range of x values and relationships between x , y and z that correspond to various subsets of the class of interest. For example, saturated, tertiary (mono)amines (STAs) have stoichiometries of the form $C_xH_{2x+3}N$, with $x \geq 3$. In cases where the validation set is relatively small, qualitative assessments are proffered.

3. EPI-SUITE MODELS: DESCRIPTION AND VALIDATION

3.1 Normal Boiling Point (NBP)

A compound's normal boiling point (NBP) is the temperature at which a compound's vapor pressure is 1 atm. By itself, a compound's NBP can be compared to the NBPs of other compounds for a preliminary ranking of its inhalation (exposure) risk. Employed as input for estimating vapor pressures at ambient temperatures - see Section 3.3 - NBPs estimates also have the potential to be used in obtaining more highly refined estimates of this risk.

The EPI-Suite program for estimating NBPs is MPBPWIN. It implements an adaptation of a group additivity model developed by Stein and Brown (Stein and Brown, 1994). The model's coefficients were

parameterized by fitting the model to the measured NBPs of a "diversely functionalized" 4426-constituent training set. Tertiary amine N-atoms are a group that is defined in the model, with the model going so far as to distinguish between "ring" and "non-ring" tertiary amines. This was taken as an indication that the model would yield reliable estimates for STMs.

Because a large number of experimentally measured STM and STA NBPs were identified, it was decided to include in the validation set only those compounds having C-atom/N-atom ratios ≤ 6 . (For a number of reasons, fuel performance is expected to degrade with increase in this ratio, and fuels with ratios exceeding 6 are expected to have no chance of meeting rocket performance requirements.) Experimentally derived NBPs for 53 STMs and STAs with C-atom/N-atom ratios ≤ 6 were identified. The NBPs for this set range from 270 to 570 K. For reference, the NBP of MMH is 361 K.

Figure 2 shows how the NBPs estimated for validation set compounds compare with their experimentally derived counterparts. All estimates are within 8% of their corresponding experimentally derived value, the RMSE value is 13, and the largest single deviation is 30 K. These results suggest that the MPBPWIN estimates for STM candidates will be reasonably accurate.

Unlike amine N-atoms, a coefficient for azides is not included in the MPBPWIN model for estimating NBPs. In the case of DMAZ, where the azide group connects to the C-atom of a primary alkyl group, it assigns the three N-atoms as $-N=$, $=NH$, and $>N<$ (+5) groups. (The assignment of one of the azide N-atoms as an $=NH$ group is puzzling.) Not surprisingly, it also produced a poor estimate - 647 K versus the measured value of 408 K.

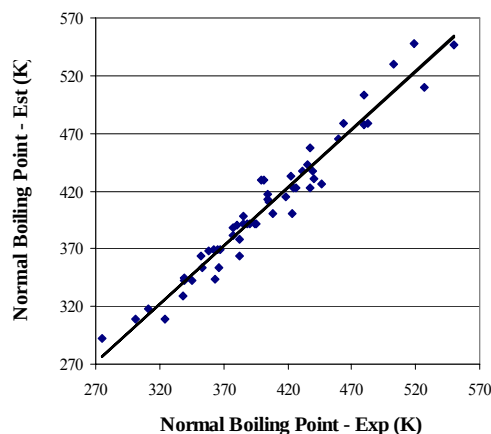


Figure 2. A comparison of MPBPNT STA and STM NBP estimates with corresponding experimentally measured values.

The model's estimates for azide *NBP*s could perhaps be improved by assembling a set of azido compounds whose *NBP*s have been measured and developing a coefficient for azido groups based on it. However, prior to undertaking such an effort, the author decided to determine whether reasonable estimates could be obtained by employing the bromine analog of an EA of interest as the input for the model. The approach was suggested by previous work showing a correspondence between the *NBP*s of azide and bromide analogs (McQuaid, 2002). To work, it was also necessary that, as is the case, primary bromine atoms be a defined group in the QSPR.

Experimentally derived *NBP*s for 5 EAs, 7 linear alkyl (mono)azides, and 4 alkyl diazides were identified. The *NBP*s for the validation set range from about 400 to 500 K. Figure 3 compares the experimentally derived *NBP*s for the azides with MPBPNT's estimates for their bromine analogs. The estimates for the 5 EAs and 7 monoazides were generally good. Shown as closed diamonds in Figure 3, the RMSE for these 12 compounds is 9 and the largest single deviation is 23 K. The estimates for the 4 diazides, which are shown as open diamonds in Figure 3, were consistently too low by about 20 K. Since diazides have been shown to have characteristics which will make them unsuitable hypergols, the indicated deficiency in the approach is not considered cause for concern. Thus, *NBP* estimates for EA candidates based on MPBPNT estimates for their bromine analogs are expected to be reasonably accurate.

3.2 Vapor Pressure (VP)

Like the model for predicting *NBP*s, the EPI-Suite models for estimating compound *VP*s (at any temperature) are accessed via MPBPWIN. Three different models are provided, but only two are applicable to STMs and EAs: (1) the Antoine method (Lyman et al., 1990) and (2) the modified Grain method (Lyman, 1985). (The program reports a "suggested" *VP* which for liquids is an average of their estimates, and it is the basis for the comparisons that follow.) Both models utilize a compound's *NBP* as the starting point for an extrapolation to the *VP* at another temperature. As such, the methods have little value for compounds whose *NBP*s have not been measured or can not be accurately predicted. But as discussed in the previous section, MPBPNT's estimates for STM and EA *NBP*s are expected to be reasonable.

Experimentally measured *VP*s for 5 STAs and 1 STM were identified. Shown in Table 1, they range from < 1 to 1610 mm Hg. The MPBPNT estimates for them are included for comparison. Since the author was inter-

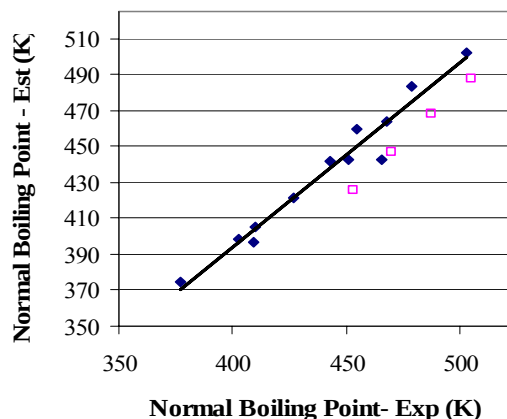


Figure 3. Comparison of experimentally measured azide *NBP*s with MPBPNT *NBP* estimates based on the bromine analogs of the azides. Closed diamonds are monoazides. Open squares are diazides.

ested in the estimation method's reliability for compounds without a measured *NBP*, even though measured *NBP*s are available for all 6 compounds in the table, the input to the model was MPBPNT's *NBP* estimate for them. For the compounds that are liquid or gas at 298 K, the estimates are within a factor of two of their measured value. This accuracy is considered sufficient for early stage screening of STM candidates.

As mentioned in the discussion of MPBPNT's *NBP* estimate for DMAZ, MPBPWIN misassigns the (core) atoms of the azido group and the *NBP* estimate for it is poor. Thus its *VP* estimates for EAs were expected to be poor, and no attempt was made to validate them. Instead, it is suggested that *NBP* estimates for EAs be employed in the Clausius-Claperyon equation along with estimates for their enthalpy-of-vaporization to obtain the *VP* estimates. This approach was employed by the author to address questions raised in the development of parameters for azide atom types in the COMPASS force field (McQuaid et al. 2004). In that work, enthalpies of vaporization for various azido compounds were derived from cohesive energy densities determined via molecular

Table 1. Experimental and Estimated *VP*s for STAs and an STM.

Compound	<i>NBP</i> (est)	<i>VP</i> (exp)	<i>VP</i> (est)
	(C)	mm Hg	
Trimethylamine (g)	18.8	1610	954
Methylpyrrolidine (l)	91.6	100	54
Triethylamine (l)	95.5	57	45
Methylpiperidine (l)	117.6	19	17
Tripropylamine (l)	164	1.5	2.1
DABCO (s)	152.5	0.7	0.1

dynamics (MD) simulations. Enthalpies-of-vaporization can also be obtained with a QSPR based on descriptors derived from quantum chemistry calculations (McQuaid and Rice, 2006). The reliability of the QSPR method for azides was validated in the course of a study to establish condensed-phase enthalpy-of-formation estimates for polyazido-functionalized compounds. Given the prior work, it is expected that EA VPs will be reasonably estimated by this method, and it is not discussed further.

3.3 Octanol-Water Partition Coefficient (K_{ow})

A compound's K_{ow} value refers to the ratio of the concentrations that will be found for it in the octanol and aqueous phases of a two-phase octanol-water mixture. The ratio provides a measure of a compound's lipophilicity and has been shown to be an indicator of a compound's propensity to accumulate in biological systems. Beyond that correlation, the parameter has been shown to correlate with many and varied toxicological endpoints for different species. Because K_{ow} values span several orders of magnitude, $\log(K_{ow})$ values are typically reported instead of K_{ow} , and that practice is followed here.

The EPI-Suite model for predicting $\log(K_{ow})$ is accessed via KOWWINNT. It is based on a group additivity model developed by Meylan and Howard (Meylan and Howard, 1995). The coefficients for the model were derived from measured $\log(K_{ow})$ values for a 2464-compound training set. Like the model for estimating NBPs, tertiary amine N-atoms are a defined group, but the model does not distinguish between "ring" and "non-ring" amines. Azides are also a defined group.

Figure 4 compares experimentally observed and estimated $\log(K_{ow})$ s for 11 compounds that are considered

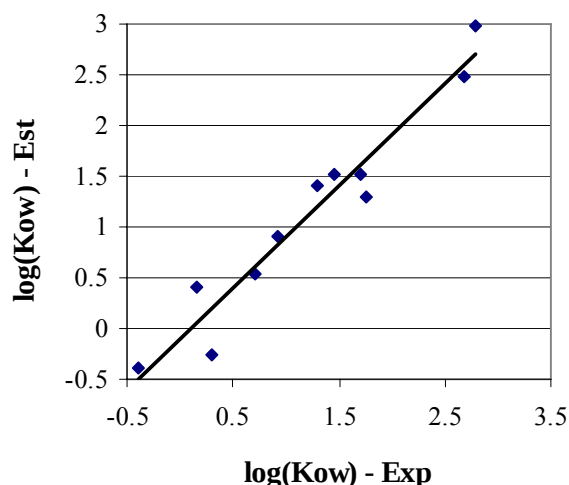


Figure 4. Comparison of experimentally measured and estimated $\log(K_{ow})$ values for STAs and STMs.

pertinent to validating the method's estimates for STMs. The $\log(K_{ow})$ values for the validation set range from -0.4 to 2.68. The RMSE is 0.26 and the largest single deviation is 0.56. These results suggest that KOWWINNT's $\log(K_{ow})$ estimates for STM candidates will be reasonably accurate.

Though azides are a defined group in KOWWINNT's model, the basis for the parameterization is uncertain. Moreover, no experimentally determined values useful for validating the model's estimates could be found. The reliability of KOWWINNT's estimates for EAs is therefore uncertain. To address this issue, ARL is considering undertaking an experimental effort that would establish $\log(K_{ow})$ values for a small set of azido-functionalized compounds.

3.4 Water Solubility (WS)

The EPI-Suite program has two modules for estimating the WS of organic compounds: WATERNT and WSKOWNT. WATERNT is based on a group additivity model similar to that in KOWWINNT. Coefficients for individual groups in WATERNT were derived from measured WSs for a 1000-constituent training set, and it was been tested on a validation set of 3,923 compounds. A coefficient specific to tertiary amine N-atoms is defined, but one for azido groups is not. In the case of DMAZ, it appears that the program mistakenly assigns the azido group as an azo group ($-N=N-$).

WSKOWNT is based on a group additivity model developed by Meylan and Howard (Meylan and Howard, 1994). In it, a compound's WS is derived from (1) a value for its K_{ow} , (2) a dependence on molecular weight, and (3) a correction based on coefficients for variously defined groups. Its equations were derived from a dataset of 1450 compounds with measured $\log(K_{ow})$ s, WSs, and melting points. It was tested against a validation dataset of 817 compounds. One of its groups is "aliphatic amines," but there is not a distinction between primary, secondary, or tertiary amines, or between "ring" and "non-ring" amines. Like WATERNT, the program (mis)identifies the azido group in DMAZ as an azo group.

Nine (total) experimentally measured WS values for STAs or STMs were identified, but their value in validating WATERNT and WSKOWNT estimates for STM candidates is limited. One deficiency is that only three values were measured at 298 K, with the others being measured at temperatures ranging from 288 K to 322 K. Since the models make no allowance for a dependence on temperature, there are few comparisons to make. That said, the values that have been obtained indicate that the WSs of STMs will be relatively high—

i.e. $\geq 1 \times 10^4$ mg/L—and the WATERNT and WSKOWNT estimates for STM candidates are observed to fall in this range. Thus these models' estimates for STM candidates are expected to be adequate for screening purposes early in the selection process.

The inability of WATERNT and WSKOWNT to properly identify the azido group in DMAZ suggests that their WS estimates for EAs will be poor, but no experimentally measured data could be found to confirm or refute that opinion. It is expected that EA WSs will be similar to those of analogous STMs. A crude experimental measurement of the WS of DMAZ indicated that it exceeded 1×10^5 mg/L. To further test the hypothesis, ARL may undertake an experimental effort to measure WSs for a small set of azido-functionalized compounds.

3.5 Air-Water Partition Coefficient (*HLC*)

The EPI-Suite module for estimating a compound's *HLC* is HENRYNT. It estimates values via two different methods: a bond contribution method (Meylan and Howard, 1991) and a group contribution method. (The basis for the group contribution method is not provided.) The bond contribution method has 59 different defined bonds, the coefficients for which were derived from measured *HLC*s for 345 organic compounds. The bond contribution method recognizes all the bonds found in STMs and EAs, and it has a specific correction for azides. The group contribution method can be used to obtain estimates for STMs but not EAs.

Five experimentally measured *HLC* values for STAs were identified. They are compared to estimates in Table 2. Estimates based on the group contribution method were obtained for 4 of them, and all are within a factor of 2 of their corresponding measured value. Estimates based on the bond contribution method were obtained for all 5, and all are within a factor of three of the corresponding experimentally determined value. It should also be noted that, as expected based on the high WSs of STAs, the *HLC* values for them and STMs are relatively low. The compounds in the validation set all had values less than 1.5×10^{-4} atm-m³/mol. Thus it is expected that HENRYNT's *HLC* estimates will be adequate for early stage screening assessments of STM candidates.

Though HENRYNT's output for an estimate for DMAZ shows the presence of a coefficient for the azide group, a search of the data set employed to develop the model was unable to identify any azide compounds in it. Thus, the basis of the coefficient is uncertain. In addition, no experimentally measured *HLC* values for azides were identified in a more general search. Thus,

the reliability of HENRYNT's *HLC* estimates for EAs remains to be verified.

3.6 Affinity for Organic Carbon (*K_{oc}*)

The parameter *K_{oc}* is defined as "the ratio of the amount of chemical adsorbed per unit weight of organic carbon (co) in the soil or sediment to the concentration of the chemical in solution at equilibrium" (Lyman et al., 1990). It provides an indication of the extent to which a chemical partitions between solid and solution phases in soil, or between water and sediment in aquatic ecosystems. Estimated values of *K_{oc}* are often used in environmental fate assessment because the measurement of *K_{oc}* is expensive. As with *K_{ow}* values, *K_{oc}* values span several orders of magnitude, and log(*K_{oc}*) values are typically reported instead of *K_{oc}* and that practice is followed here.

The EPI-Suite module for estimating *K_{oc}* is PCKOCWIN. The estimation of *K_{oc}* is based on a correlation with the first-order molecular connectivity index (1-MCI) and adjustments based on coefficients specified for various bonds (Sabljic, 1984, 1987; Bahnick and Doucette, 1988). C-N (single) bonds are among those for which a coefficient is specified, suggesting PCKOCWIN is appropriate for use in estimating the log(*K_{oc}*)s of STMs. That is not the case for EAs, where as with WATERNT and WSKOWNT the program (mis)identifies the azido group of DMAZ as an azo group.

No experimentally measured log(*K_{oc}*) values for "small" STAs, STMs, or EAs could be identified. The training set from which the model was developed does contain compounds with amine groups, but the molecules are relatively large, and their log(*K_{oc}*) values tend to fall in the range from 1.0 to 4.0. The values for small STMs on the other hand, tend to be much higher. For example, the estimate for TMEDA is 64. While this might be taken to imply that the log(*K_{oc}*) values of STMs are very high, and thus perhaps not in need of being estimated, it may be that the model is breaking down. Thus, further investigation of this issue is recommended.

4.0 SUMMARY

To facilitate the development of hypergols that pose less threat to US Army soldier health and their training environs than MMH, the validity of EPI-Suite QSPRs for estimating properties needed to model the fate, transport and effect of candidates was evaluated. Six properties were of interest: normal boiling points, (ambient) vapor pressures, octanol-water partition coefficients, water solubilities, air-water partition coefficients and affinity for organic carbon. For candidates that can be classified as saturated, tertiary multiamines, the validity of EPI-

Suite QSPRs for estimating 5 of the 6 properties could be confirmed. The exception was the QSPR for estimating their affinity for organic carbon. In this case, no data which could be employed to validate the model could be found. Means for addressing this issue need to be identified. For candidates that can be classified as ethanamine azides, the EPI-Suite QSPR estimates for the 6 properties were either poor, or experimental measurements to which they could be compared could not be identified. An alternate method for estimating the normal boiling points and vapor pressures of ethanamine azides is available, but experimental measurements will probably need to be undertaken so that QSPRs for the other 4 properties can be developed.

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