To: Ad Hoc Subcommittee, Air Pollution Control Board *and*
Air Management Services Division

From: Adam M. Finkel, Sc.D., CIH
Date: November 4, 2010
RE: Rationale for, and Derivation of, Performance Standards for *n*-propyl bromide (nPB) in Co-commercial Dry Cleaners

After considering the June 2010 report "Increased Toxicity and Carcinogenicity of *N*-Propyl Bromide (1-Bromopropane) Relative To Perchloroethylene" (Finkel 2010a), the Air Pollution Control Board (APCB) moved to ban the use of *n*-propyl bromide (nPB) in dry cleaning. Such a ban is justified by the available scientific evidence, and is a reasonable way for a regulatory agency to handle the vexing problem of "adverse substitution" of a more toxic chemical for a less toxic one: control the latter, while banning the former. However, quantitative risk assessment (QRA), a well-accepted scientific methodology, is founded on the premise that zero risk is often unattainable, and is often not necessary to protect the public, because enforcement of health-protective numerical standards (derived using QRA) can provide ample protection.[1]

Indeed, the City was guided by QRA principles when it established performance standards for perchloroethylene ("Perc") that allow its continued use in co-commercial facilities.[2] The 40 ppb performance standard for "chronic" exposure was based on the application of standard non-cancer risk assessment methods to a human neurotoxicity study (Ferroni et al., 1992) that showed measurable neurologic deficits upon chronic exposure to 3.6 ppm Perc (that is, 15 ppm in the workplace, adjusted from a 40 hour/wk

[1] "Ample protection" has two different meanings if one believes that carcinogens and non-carcinogens have very different dose-response relationships. For the former, "ample protection" would mean an assessed probability of harm that is very small (say, 1 chance in 1 million, which is a common benchmark used by EPA and other agencies). For the latter, many scientists believe that there exist exposure levels that are low enough to fall below biological thresholds for most or all of the individuals in the exposed population—that is, zero risk with non-zero exposure. This distinction, however, is increasingly being challenged (see, e.g., Chapter 5 of the recent National Academy of Sciences report **Science and Decisions: Advancing Risk Assessment**), but a "unified" view of cancer and non-cancer dose-response also accepts that sufficiently low exposures (of either type) can be associated with acceptably low probabilities of harm.

[2] Limiting the QRA-based performance standards to co-commercial facilities reflects the very reasonable science-policy judgment that schoolchildren, the infirm, and residents deserve additional protections that a non-zero exposure limit cannot by definition provide.

scenario to a continuous 168 hour/wk scenario: (15 x (40/168) = 3.6)). This level also corresponds to the chronic "minimal risk level" set by the U.S. Agency for Toxic Substances and Disease Registry (ATSDR). At the 40 ppb level, as I noted in my January 2010 report "Evaluation of Perchloroethylene Risks and the Philadelphia Dry-Cleaning Proposal" Report (Finkel 2010b), continuous lifetime exposure would correspond to an excess cancer risk of between $6x10^{-4}$ and $6x10^{-3}$ (if we make use of all the large amount of information on the pharmacokinetics of Perc metabolism in rodents and humans), or a cancer risk of about $6x10^{-5}$ if we interpret the rodent tumor data without a pharmacokinetic adjustment (see below).

The City also decided that at a higher measured Perc value in the co-located facility (200 ppb), the cleaner responsible would have to shut down until the contamination was remedied, rather than having 30 days to control the situation as would be the case if the concentration in the adjacent facility was above 40 ppb but below 200 ppb. This "subchronic performance standard" of 200 ppb was derived from a short-term study in humans, as interpreted by the ATSDR.[3]

Finally, the City decided that dry cleaners using Perc must remediate when they detect fugitive emissions from a Perc machine in excess of 25 ppm. This standard mirrors the 25 ppm leak detection standard that the U.S. EPA established for dry cleaners ("National Perchloroethylene Air Emission Standards for Dry Cleaning Facilities," 70 *Federal Register* 75884-75906, 12/21/05). 25 ppm is also the current Threshold Limit Value (ACGIH TLV®) for Perc.

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[3] The ATSDR based their Minimal Risk Level here on a human study by Altman et al. (1992), (Neurobehavioral and neurophysiological outcomes of acute repeated perchlorethylene exposure. Applied Psychology: An International Review 41(3)269-279). In that study, subjects exposed to 50,000 ppb Perc for 4 hours over 4 days experienced decreased vigilance, eye-hand coordination, and increased latency of visual evoked potentials. Adverse effects were not reported for those exposed to 10,000 ppb. Therefore, a LOAEL of 50,000 ppb and a NOAEL of 10,000 ppb were established in this study. After adjusting the NOAEL to extrapolate from intermittent exposure (the 10 ppm concentration was multiplied by 4/24 hours) and applying a 10-fold safety factor to account for human variability, the resulting MRL is 200 ppb.

Each of these three types of numerical limits can, of course, also be derived for nPB.[4] Every toxic substance is different, and we know more quantitative details about the toxicity of some substances than we do about others, but one of the virtues of QRA is that it can take both of those kinds of distinctions into account. As a logical matter, there are really only two legitimate ways to approach the task of setting the main (chronic) performance standard for nPB, in light of the fact that as of 2010, we know a great deal about its toxicity and carcinogenicity, but still not as much as we know about Perc (a solvent that has been studied for many more years). I carefully considered these two conceptually different ways to set the main nPB performance standard: (1) by addressing the *relative* question of whether nPB is less or more dangerous (at any equivalent dose) than Perc is; or (2) by addressing the *absolute* question of exactly how potent a neurotoxin and a carcinogen nPB is, without considering it vis-à-vis Perc.

As my June report (Finkel 2010a) stated in detail, we now know a great deal about nPB's neurotoxicity in humans and animals, and we now have a complete rodent cancer bioassay on nPB. As that report summarized, the cancer bioassay shows clear evidence of carcinogenicity in two different sex/strain/tumor combinations (female rat intestine and female mouse lung), and some evidence of carcinogenicity in several others (male rat intestine and skin). Even more significantly, in comparing the most definitive bioassay result in the Perc and nPB studies, the Perc study showed a significant increase in tumors at the lowest dose tested (50 ppm), but against a fairly high background rate (14 leukemias at 50 ppm versus 11 in the control group; all results out of 50 animals per group). For nPB, on the other hand, there were 9 female mouse lung tumors at 62.5 ppm, versus only 1 in the control group. At comparable doses, therefore, nPB causes a far more significant response than does Perc. The human neurotoxicity information on nPB consists of several studies documenting serious and irreversible neuropathy in disparate cohorts of workers exposed to roughly 75-200 ppm nPB (see, e.g., Majersik et al. 2007,

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[4] Setting performance standards in lieu of a ban creates a "level playing field," both in terms of the science used (to the extent that non-zero exposures to nPB can be considered to pose an acceptably low risk, it is not penalized relative to Perc) and in terms of business decisions (if cleaners find it easier or less expensive to use nPB, and can do so while providing an equivalent amount of protection to co-located citizens, this approach allows them to make such a choice).

Raymond and Ford 2007, CDC 2008), as well as several studies (Ichihara et al. 2004a, Li et al. 2010a, Li et al. 2010b) showing less severe, but significant, quantitative neurological deficits in workers exposed to averages of roughly 1-3 ppm nPB.

I remain very confident, as a scientific matter, that the answer to the question "is nPB a more potent neurotoxin (more potent carcinogen) than Perc?" is "yes" on both counts. I see no reason at present not to accept the NTP bioassay at face value (that is, to invoke some as-yet unarticulated theory as to why the rodent tumors should be questioned as relevant to humans), the neurotoxicity case series document severe effects not seen in workers exposed to comparable high doses of Perc, and the case-control studies attest to measurable deficits similar to the major studies of Perc, yet at somewhat lower exposures. Comments critical of these conclusions from Finkel 2010a have been submitted by representatives of the nPB solvent industry. However, as addressed in a supplemental report ("Perspectives on nPB Neurotoxicity and Carcinogenicity in Light of New Evidence and New Challenge," Finkel 2010c), these comments do not change my prior analysis in any material way, whereas some new evidence reinforces the prior analysis.

Nevertheless, we cannot be as confident in *how much more toxic nPB is than Perc* as we can be in the qualitative rank ordering (nPB>Perc). Put another way, I am confident that any future ASTDR Minimal Risk Level for nPB, and/or any EPA Reference Concentration for nPB[5], should be **lower** than the 40 ppb limit (ATSDR MRL) and the 2 ppb limit (EPA RfC) that have been set for Perc—but **how much lower** I cannot predict with much precision.

Therefore, I present here a main recommendation and an ancillary recommendation for the chronic performance standard. My main recommendation is as follows:

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[5] Contrary to the assertions by the nPB manufacturers, there is no EPA RfC for nPB. The substance has not been nominated for toxicological assessment under the EPA Integrated Risk Information System. I have directly communicated with both IRIS managers and senior EPA officials in the Office of Air and Radiation about this, and they confirm that EPA has no plans currently to develop an RfC. There are ample data with which to do so; the RfC program is simply facing a backlog of substances for which RfCs are already in active development.

- Because nPB is a more potent neurotoxin and more potent carcinogen than Perc, 40 ppb is the *highest* sensible performance limit for nPB that would be necessary to ensure that chronic health risks to Philadelphia residents and workers do not *increase* as a result of cleaners switching from Perc to nPB. It is an appropriate science-policy judgment to control nPB at least as stringently as Perc, as an alternative to an outright ban. I note two important consequences of a 40 ppb standard for nPB. First, for nPB the human Lowest Observed Adverse Exposure Level (LOAEL) for chronic neurotoxicity is either 2.9 ppm (from Ichihara 2004a)[6], 1.3 ppm (if the brand-new Li et al 2010 study is used), or 2.8 ppm (if another new article by Li et al. with an English-language abstract but a Chinese-language text[7] is used). All three of these values are quite consistent with each other. When you convert from workplace exposure (40 hrs/week) to continuous exposure (168 hours/week), 2.9 ppm is equivalent to 700 ppb continuous exposure (2900 ppb x (40/168) = 690 ppb). So, a 40 ppb limit provides a margin of safety roughly 20-fold below the LOAEL (700/40 = 17.5). This is not as protective as the 100-fold factor EPA or ATSDR would use when starting from a human occupational LOAEL, but it is in my opinion a reasonable and defensible limit under the circunstances. Secondly, at 40 ppb, I calculate the excess lifetime cancer risk from nPB (using the NTP bioassay results from female mouse lung tumors) to be approximately 8×10^{-5}—that is, a risk of 8 per 100,000. Again, this is substantially higher than the 1-in-1-million level typically used to demarcate a

[6] Note especially that the subsequent study (Ichihara 2004b) involved no measurements of neurological deficits, and therefore cannot contradict the findings from the same group earlier that year. For a detailed discussion of the two 2004 studies, see Finkel 2010c.

[7] W.H. Li et al. (2010b). "Effects of 1-bromopropane on Neurological and Hematological Changes of Female Exposed Workers," *Zhonghua Lao Dong Wei Sheng Ye Bing Za Zhi*, May, **28(5):** 339-334. English abstract available at http://www.ncbi.nlm.nih.gov/pubmed/20853682. The abstract states that at a geometric mean concentration (8-hour TWA) of 14.08 mg/m^3, which is the same as 2.82 ppm, exposed workers showed significantly decreased nerve conduction velocities (motor and sensory nerves), reduced vibratory sense, and neurobehavioral disturbances.

"de minimus" acceptable risk level, but it is in my opinion a reasonable and health-protective limit for this health endpoint.[8]

The other conceptual approach to setting a chronic performance standard would be to use the human neurotoxicity data on nPB exactly as ATSDR used such data on Perc, even though it could be argued that the nPB studies are newer and not as definitive. As discussed above, of the three most recent such studies on nPB, all showed various neurological deficits (via quantitative measurements, not symptom surveys) at roughly 3 ppm exposure in the workplace. Assuming 40 hour/week occupational exposure, (3000 ppb x (40/168)) equates to roughly 700 ppb continuous exposure. Just as ATSDR did for Perc, it would be standard scientific procedure to apply one 10-fold safety factor to adjust from a LOAEL to where the No Observed Adverse Effect Level (NOAEL) would be assumed to be, and another 10-fold factor to account for persons of above-average susceptibility relative to the average susceptibility of a small group of workers studied. This approach would yield a "chronic performance standard" of **7 ppb** for nPB. However, I recommend that Philadelphia use the 40 ppb limit instead, for the reasons stated above.

As for a higher "acute concentration limit," a concentration of **225 ppb** for nPB can be derived as follows. In the 2009 NTP report, a 3-month study in rats (and mice) was conducted along with the 2-year chronic studies. In male rats, significant toxic effects (primarily, vacuolization of the liver) were observed at 250 ppm (and higher), but not at 125 ppm (the next lower dose), making 125 ppm a subchronic NOAEL. As the

[8] I emphasize that it is unavoidably difficult to directly compare the carcinogenic potencies of Perc and nPB using the most detailed techniques available. In my January 2010 Report on Perc, I used the pharmacokinetic adjustment that EPA developed in great detail—but such an adjustment is impossible for nPB due to the lack of any data or models of comparative pharmacokinetics at present. The human carcinogenic potency of nPB, like that of Perc, might increase once pharmacokinetics are taken into account, but that conclusion must await data collection and analysis. The only sensible chemical-to-chemical comparison is to calculate the "slope factor" for each without any pharmacokinetic adjustment, which is what I have done here, and which indicates nPB is roughly 34 percent more potent than Perc. In any event, nPB clearly causes far more excess tumors relative to the control group, at lower doses, than Perc does (that is to say, the nPB slope is *far* less possible to be a chance finding than the Perc slope).

APCB did to derive the Perc limit, one first could adjust the dosing pattern (in this case, 30 hours/wk) to an equivalent concentration for continuous exposure (168 hours/wk)—this yields a continuous-equivalent NOAEL of 22.5 ppm. The standard safety factor in this case is 100 (10 fold to extrapolate from rats to humans with a margin of safety, and 10 fold for human interindividual variability). This would yield a concentration of 225 ppb.

Finally, I recommend that AMS establish a leak detection benchmark of 10 ppm for nPB. Because EPA's national standard for Perc has a 25 ppm leak detection benchmark, and the ACGIH TLV for Perc is also set at 25 ppm, the fact that the current TLV for nPB is 10 ppm supports this decision.

A Note on "Feasibility":

Whenever a federal, state, or local agency sets a concentration limit, the best evidence for or against whether it is feasible to achieve that limit comes from actual measurements of like facilities, which can be "well-controlled," poorly-controlled, or both, depending on available information. But if a particular limit is both feasible and *already being achieved* everywhere one has looked, it could be argued that the limit is feasible but *unnecessary* because no facilities would have to improve their performance (or, of course, one could argue that a lower limit might be both feasible and necessary, depending on the risk assessment). On the other hand, the more the measured levels exceed the proposed limit, the greater the need for the regulation—if it can be achieved, then clearly there will be significant exposure reductions if it is promulgated and enforced. So as a logical matter, there are only three possible results of comparing a proposed limit to what is being achieved in practice (assuming, as is the case here, that risk assessment information suggests the need for a limit roughly this protective): (1) both the well-controlled and the poorly-controlled facilities achieve performance lower than the proposed limit—in which case common sense would argue that the limit is *clearly feasible but possibly unnecessary*; (2) neither the well-controlled nor the poorly-

controlled facilities can achieve the limit, in which case one would conclude that the limit is *clearly necessary but only possibly feasible;* or (3) the well-controlled facilities come in under the limit but the poorly-controlled ones (greatly) exceed it, in which case one would conclude that the limit *is both clearly feasible (it can be achieved) and clearly necessary (it is not being achieved elsewhere).* **The data submitted to AMS and already in the record clearly indicates that the third situation applies to dry cleaning and nPB:**

The data submitted by EnviroTech indicates that with careful engineering and monitoring, dry cleaners can achieve nPB levels within their facilities of roughly 1-5 ppm. In one of EnviroTech's two memoranda (Mark Stelljes to Rich Morford, undated), a sample registering 16 ppb (well below the 40 ppb performance standard) was documented outside the front door of the facility. Presumably, this value would have been lower within any co-located adjacent facility.

On the other hand, data from NIOSH (CDC 2010) and from Blando et al. (2010) clearly indicates that without hands-on support from the manufacturers or similar levels of vigilance, dry cleaners using nPB can experience *much* higher emissions. The NIOSH evaluation found levels of from 10 to 56 ppm inside dry cleaners, while the Zhang et al. study documented 8-hour TWAs of from 1 to 55 ppm. As these levels are roughly 10-fold higher than what EnviroTech could achieve in their test facility in Sacramento, it is logical to assume that levels immediately outside such poorly-controlled facilities would exceed 160 ppb.

In short, the first set of data documents the *feasibility* of a 40 ppb standard; the second (and more extensive) set documents the *need* for it.

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