HARC NEWS

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THE USE OF PHARMACOKINETICS AND THE PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL TO DETERMINE ALLOWABLE EXPOSURE TIMES FOR HALOCARBON AGENTS IN THE NFPA 2001 STANDARD

QUESTIONS AND ANSWERS

The 2000 Edition of the *NFPA 2001-Standard on Clean Agent Fire Extinguishing Systems* incorporates the use of pharmacokinetics and the physiologically-based pharmacokinetic (PBPK) model as an option for determining allowable exposure times for halocarbon agents such as FM-200 and FE-227 (HFC-227ea), FE-25 (HFC-125), FE-36 (HFC-236fa), and CF_3I (FIC-13I1). Although the use pharmacokinetic modeling is quite common for determining safe exposure to chemicals in air, water and the workplace, this is the first use of PBPK in a fire suppression agent standard. In an effort to provide a basic understanding of the science behind the use of PBPK, we have prepared answers to some of the basic and most frequently asked questions.

1. What does PBPK stand for?

The initials stand for **P**hysiologically-**B**ased **P**harmaco**k**inetic and Table 1 contains definitions of these terms ….

Table 1
Definition of Terms

Term	Definition
Physiologically	Of or relating to physiology.
Physiology	A branch of biology that deals with the functions and activities of life or of living matter (as organs, tissues or cells) and of the physical and chemical phenomena involved.
Pharmacokinetics	The characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism and excretion.

2. What does the PBPK model do?

The PBPK model is a scientific approach for determining safe human exposure limits – both with respect to concentration level and exposure time. Its importance is that it adds the time dimension to the safe exposure criteria - a dimension which heretofore had not been a consideration with the gaseous halon alternatives.

3. Is the PBPK model for halocarbon and inert gas agents?

No – the use of the model is limited to the halocarbon agents where cardiac sensitization is the main exposure issue. With the inert gases, the exposure issue is hypoxia – or oxygen deprivation.

4. What did we do before the model?

Prior to the PBPK model, the human exposure rules have been based exclusively on exposure testing of the various halocarbon agents using dogs as the subjects. The results of the dog exposure testing were translated directly into exposure definitions NOAEL (no observed adverse effect level) and LOAEL (lowest observed adverse effect level). These agent in air concentration limits – without regard to exposure times – were then the basis for regulating which agents were suitable for use in occupied spaces and which agents were not.

5. How do we know the animal testing is conservative?

This type of testing is very conservative as the test animals are highly sensitized to the cardiac effects of the halocarbon agents by being injected with epinephrine (synthetic adrenaline) to levels several times greater than that which could be naturally produced. In every case where the test animal was exposed to the agent without the use of epinephrine, the animal has been able to tolerate much higher levels of agent concentrations before a cardiac event. Thus this cardiac sensitization with epinephrine predisposes the test animals to a cardiac event at lower agent concentrations than is the case without the epinephrine challenge.

6. What's wrong with a strict application of the NOAEL and LOAEL?

The difficulty caused by literally interpreting the results of the dog exposure tests and applying them to exposure limits for humans is that the approach does not take into account the physiological differences between dogs and humans. The No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effects

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Level (LOAEL) type testing are "external" experiments where the animals are exposed to varying levels of agent concentrations after epinephrine challenges in an effort to discover the NOAEL and the LOAEL. In that type of testing, nothing is done to relate the cardiac sensitization event with an "internal" measure of the chemical that actually gets into the body during the exposure. In contrast, the PBPK model requires that the concentration of the extinguishing agent in the blood stream of the test animal be measured as that is relevant information that can applied to humans. Thus, the direct application of the results of the NOAEL / LOAEL testing on animals to establish safe exposure limits for humans – without regard for the difference in the pharmacokinetics of the two species – can result in exposure limits that are unnecessarily understated or inappropriately overstated.

7. Okay, so what can we do with the PBPK model?

Since 1995, there has been much work to develop this more scientific basis for determining safe exposure levels for humans. What has evolved from this work is a PBPK model which bridges the gap between the animal tests and the application of those results to establish safe, short term human exposure guidelines. The PBPK model lets us use the NOAELs and LOAELs determined for the cardiac endpoint in test animals and couple that with what we know about the physiology of humans. Using this approach we can then establish safe human exposure limits, both in terms of agent concentration levels and exposure times.

8. What are the NOAEL and LOAEL values for halon 1301?

The NOAEL and LOAEL are approximately 5% and 7.5% respectively.

9. Those numbers sound low – what does that mean?

It means that a strict interpretation of the NOAEL and LOAEL for halon 1301 would not allow its use in normally occupied spaces at concentrations over 5%. For all practical purposes, halon 1301 would have been relegated to use in spaces that are not normally occupied.

10. How can this be? This is inconsistent with 30 years of safe use of halon 1301.

That's the whole point – the strict interpretation that we have used for the halocarbon alternatives is harsh and unnecessary based both on the science provided by the PBPK model coupled with the 30+ years of safe experience with halon 1301. We've used halon 1301 in normally occupied spaces at concentrations of 6-7% and higher without reports of adverse effects.

11. Why do we need the model?

The model is necessary so we can – with a strong basis in science – apply the results of the cardiac testing on animals to establishing safe exposure limits for humans. Table 2 is an illustration of how the animal testing and PBPK modeling are actually complementary efforts that rely on each other to reach a scientific conclusion.

Table 2
Testing Versus Modeling

Testing / Modeling	What It Does and Does Not Accomplish
Animal Testing to Establish NOAEL and LOAEL	This testing does little more than establish the NOAEL and the LOAEL for the species of the test animal after the animal has been challenged with a level of epinephrine well above any that could occur naturally in the body. This type of animal testing ignores the differences between the physiology of the test animal and humans with respect to the rate of absorption of the agent into the blood via the lungs and the rate of transport of that absorbed chemical to the heart.
Animal Testing to Establish Agent Levels in the Blood of the Test Animals	Gives a conservative indication of the minimum level of the agent in blood of the test animal at which a cardiac event may occur. The relationship between chemical agent concentration in the blood and cardiac sensitization events can be used as the basis for establishing safe exposure levels.
PBPK Modeling	The PBPK modeling allows us to predict the rate of absorption of various agents into the blood stream of humans via the lungs. The concentration of agent in blood at any given time during the exposure can be compared to the concentration of agent in blood determined to be associated with cardiac sensitization events. If the agent concentration in blood is below that associated with cardiac sensitization events then the exposure conditions (concentration and time) would be considered safe for humans. The PBPK model must rely on the end point (concentration of agent in the blood stream) determined in the animal testing;the model does not derive different end points or target blood levels.

12. Are we getting less safe using the model?

Absolutely not. What the PBPK model does is bring science to a somewhat incomplete process that had been the sole basis for determining safe exposure requirements. We still rely on the very conservative animal testing techniques to establish the target agent concentration in the blood stream that could be sufficient to cause an adverse cardiac event. But to be even more conservative (protective), it is recognized that people vary in their sensitivity to these types of agents. To deal with this, the PBPK process requires that a statistical

method (Monte Carlo simulations) be run to identify the safe exposure levels and times for those humans most sensitive to the agent in question. The PBPK model process then requires that only the sensitive human population is used for setting safe exposure levels. By scientifically adapting the results of the cardiac testing of animals to humans plus basing the exposure limits (agent concentration and time) on the most sensitive of the population, the PBPK model provides us with a means to establish safer exposure guidelines than those based on only the literal interpretation of the results of the animal testing.

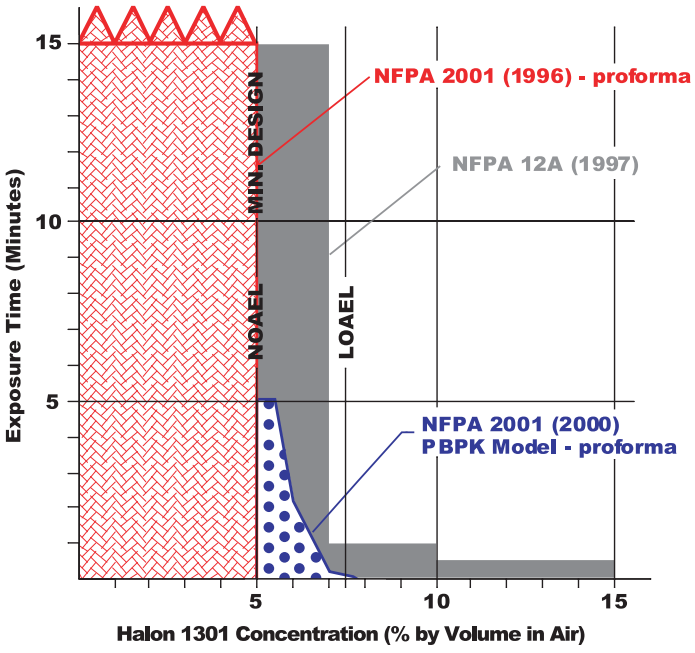
13. How much work has been put into the model?

Since 1995, there has been much work to develop this more scientific basis for determining safe exposure levels for humans. This need for the work was spearheaded by the EPA with most of the actual research and development done by the U.S. Air Force at the Toxicology Division of the U.S. Air Force's Armstrong Laboratory. In addition, the agent manufacturers invested heavily in testing to measure the data peculiar to their respective agents. By some estimates, this entire effort has had an out-of-pocket cost over $2 million.

14. How can I be sure that it's conservative?

The best way to get comfortable with the PBPK model is to look backwards at what we've done – safely – with halon 1301 for 30+ years. Then, to compare those practices with what halon 1301 would have been held to under the strict interpretation of the animal testing and what the PBPK model would tell us is a safe practice for the use of halon 1301 around humans. Figure 3 is an illustration of these various exposure guidelines.

Figure 3
Different Views on Safe Exposure Limits for Halon 1301



The green crosshatched area in the illustration shows us the acceptable human exposure guidelines for halon 1301 as describes in NFPA Standard 12A – that is, from 0 – 7%, exposure time should be no longer than 15 minutes; from 7 – 10%, exposure times should be less than 1 minute and for 10 – 15%, the exposure time should be less than 30 seconds.

The application of the strict exposure rules in the 1996 version of NFPA Standard 2001 to halon 1301 would have produced the red crosshatched area – that is halon 1301 can be used in occupied spaces up to a 5% concentration and not at higher concentrations. The blue crosshatched area represents what the PBPK model tells us about safe human exposure concentrations and time.

The fact that the PBPK model guidelines (blue crosshatching) fall well within the 30+ years of safe experience with halon 1301 (green crosshatched area) is compelling evidence that the PBPK model is a safe, conservative tool.

15. What does NFPA Standard 2001 say about the PBPK model?

The standard has changed in two areas:

- first, it permits the use of halocarbon systems for spaces that are normally occupied, designed to concentrations above the NOAEL and up to the LOAEL as long as means are provided to limit exposure to no longer than the PBPK model time corresponding to the given design concentration.
- second, it places new restrictions on the use of halocarbon systems in spaces that are not normally occupied where the system is designed to concentrations above the LOAEL and where personnel could possibly be exposed. In those instances, means must be provided to limit exposure times using the PBPK model.

16. What agents have been tested and have PBPK models?

The NFPA 2001 Standard contains PBPK model data for four halocarbons: HFC-125, HFC-227ea, HFC-236fa and FIC-13I1.

17. How do I deal with an agent that does not have a PBPK model

In the absence of the PBPK model information, the NFPA 2001 standard requires the following:

- Where egress takes longer than 30 seconds but less than one minute, the halocarbon agent shall not be used in a concentration exceeding its LOAEL;
- Concentrations exceeding the LOAEL are permitted only in areas not normally occupied by personnel provided that any personnel in the area can escape within 30 seconds. No unprotected personnel shall enter the area during agent discharge.

18. What are other standards making organizations doing about the model?

The United States has presented an information paper on the PBPK model to the Fire Protection Sub-Committee of the International Maritime Organization to start the process toward adoption of the model. The United States delegation to ISO/TC21/SC8 will be introducing the PBPK model for consideration during the next cycle for the standard for gaseous fire extinguishing systems.

19. Where can I learn more about the model?

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