

# THE TOXICITY OF REFRIGERANTS

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This paper presents toxicity data and exposure limits for refrigerants. The data address both acute (short-term, single exposure) and chronic (long-term, repeated exposure) effects, with emphasis on the former. The refrigerants covered include those in common use for the last decade, those used as components in alternatives, and selected candidates for future replacements. The paper also reviews the toxicity indicators used in both safety standards and building, mechanical, and fire codes. It then outlines current classification methods for refrigerant safety and relates them to standard and code usage.

## INTRODUCTION

Most of the dominant refrigerants for the past fifty years have been or are being replaced, to protect the stratospheric ozone layer or as a precaution to address global warming. Much to the credit of the air-conditioning and refrigeration industry, both chemical and equipment manufacturers have resisted compromise to either safety or performance in developing replacements. None of the alternative refrigerants that have been commercialized are highly toxic or even toxic, as classified by federal regulations.<sup>1</sup> Scrutiny of the new refrigerants shows them to be as safe or safer than those they replace.<sup>2</sup> Still, safety concerns have surfaced as significant factors in regulations for the new refrigerants. These concerns do not arise from increased hazard levels, but from lack of familiarity and necessary information. The rapid phaseout schedule for chlorofluorocarbon refrigerants required introduction of new chemicals before complete data were available.

Most of the early refrigerants — before the 1930s — were flammable, toxic, or both. The advent of fluorochemicals ushered in a new era of safety, as illustrated by the dramatic demonstration by Thomas Midgley in April 1930.<sup>3</sup> In announcing the development of fluorochemicals to the American Chemical Society, he inhaled R-12 and blew out a candle with it. Although this dramatic performance suggested that the new refrigerant was neither toxic nor flammable, it would clearly violate current safety practices.

As subsequent testing established the low toxicity of the new refrigerants, recognition evolved that the primary safety risks were the pressure hazards inherent to any compressed gas, asphyxiation from possible displacement of air, and frostbite with skin contact at low temperatures. These concerns were, however, common to the volatile compounds used before fluorochemicals. As the level of safety improved, so did expectations. Rules evolved to also address acute exposure hazards under emergency conditions, for example potential decomposition in fires into carbonyl halides as well as hydrochloric and hydrofluoric acids. Likewise, safety provisions also addressed the potential for cardiac sensitization and the effects of chronic exposures for both technicians and building occupants. The resulting regulations restricted the use of refrigerants, set quantity limits in occupied areas, imposed isolation requirements for refrigerant-containing components and machinery rooms, and prescribed a range of detection, ventilation, pressure relief, emergency discharge, and other safety provisions.

More recent focus on the effects of refrigerants on the environment spawned two significant safety measures, namely system tightening and modification of service practices to reduce venting. While their motivation was environmental protection, to curtail avoidable emissions, the result also lowers the likelihood and concentrations of refrigerant exposures.

## CODE ACCEPTANCE OF ALTERNATIVE REFRIGERANTS

International treaties, most noticeably the Montreal Protocol and Framework Convention on Climate Change, have focused on the global issues of environmental protection, information sharing, and assistance to developing countries. These treaties, and revisions to them, have fostered scientific assessments and set phaseout schedules for substances of concern. While federal laws govern the production and trade of alternative chemicals, most ordinances for application of refrigerants are adopted and enforced at the local level. They are included in building, mechanical, and fire safety codes, which govern building construction, system installation, equipment operation and maintenance, system modification including refrigerant conversion, and ultimate demolition. Although most are based on national or regional model codes, the introduction of alternative refrigerants occurred so rapidly that the cautious process of regulatory revision has not caught up yet. One cause of delay has been the time needed to complete toxicity tests, publish the findings, modify impacted standards, develop and adopt code revisions, and prepare design professionals, contractors, technicians, and building and fire prevention officials.

## Toxicity Testing

Facing unprecedented testing and phaseout requirements, the chemical industry formed an international consortium to accelerate the development of toxicology data for substitute fluorocarbons, both for refrigerant and other uses. The cooperative effort, named the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT), was sponsored by the major producers of chlorofluorocarbons (CFCs). The PAFT research entailed more than 200 individual toxicology tests, by more than a dozen laboratories in Europe, Japan, and the United States. The first tests were launched in 1987, to address R-123 and R-134a (PAFT I). Subsequent programs were initiated for R-141b (PAFT II), R-124 and R-125 (PAFT III), R-225ca and R-225cb (PAFT IV), R-32 (PAFT V), and — still underway — the mechanistic, metabolic, and pharmacokinetic aspects of the toxicology of fluorocarbons.<sup>4,5</sup> Extensive additional data were developed, or contributed from prior tests, by individual chemical manufacturers.

The tasks of assembling and interpreting the resultant data were expanded by the need, in some cases, to collect comparative information for the refrigerants being replaced. Whereas their introduction largely preceded the more rigorous, current testing and classification requirements of the codes, the amount of information needed was significant.

## Safety Standards

Most code provisions for refrigerant and refrigeration-system safety can be traced to either ASHRAE Standard 15, *Safety Code for Mechanical Refrigeration*,<sup>6</sup> or to general code provisions developed for occupancies where more hazardous materials are used. Standard 15 prescribes safeguards for design, construction, installation, and operation of refrigerating systems.<sup>7,8</sup> Many of the specific requirements are based on safety classifications from Standard 34, *Designation and Safety Classification of Refrigerants*.<sup>9,10</sup> This standard is the definitive source for assignment of refrigerant number designations. It also provides a safety classification system and assigned classifications.

An effort is underway, by the committees responsible for the two standards, to move determination of data needed for Standard 15 into Standard 34, and to rewrite the application requirements in Standard 15 parametrically, based on the referenced data. In doing so, the committees are refining the methods to determine refrigerant quantity limits for occupied areas, both to increase consistency and to take advantage of the new data and understanding. They also are addressing the toxicity, flammability, and fractionation concerns arising from use of zeotropic and azeotropic refrigerant blends.

## Parameters

Building, fire, and mechanical codes vary throughout the United States. They are based on state or local amendments to regional model codes or, in a few locations, locally-developed codes. Nevertheless, the data needed for compliance are fairly consistent. They include:

**LC<sub>50</sub>:** The "lethal concentration for 50% of tested animals," sometimes referred to as the *median lethal concentration*, is a primary measure of acute toxicity by inhalation of gases. It most commonly is measured with rats for exposures of four hours. A number of federal regulations (e.g., reference 1) and most building, fire, and mechanical codes deem substances to be toxic for one-hour LC<sub>50</sub> concentrations of 200 - 2 000 ppm and highly toxic for less than 200 ppm.\* Typical LC<sub>50</sub> concentrations for one hour are double those for four hours.<sup>11,12</sup> Multipliers of 1.6-4 have been suggested,<sup>13,14</sup> and one study found a range of 1.5-5.7 for 20 tested chemicals.<sup>15</sup> None of the refrigerants identified in table 1, or blends of them, qualify as toxic or highly toxic based on the LC<sub>50</sub> data and the stated criteria.

**IDLH:** The concentration deemed to be "immediately dangerous to life and health," set by the National Institute for Occupational Safety and Health (NIOSH). This measure was initially developed as a criterion for respirator selection in the 1970s as part of the Standards Completion Program (SCP). The SCP definition for IDLH was "the maximum concentration from which, in the event of a respirator failure, one could escape within 30 minutes without a respirator and without experiencing any escape-impairing (e.g., severe eye irritation) or irreversible health effects." The 1994 revision defines an IDLH condition as one "that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment." The revised and added IDLHs in 1994 are based on additional toxicity criteria and data. Whereas the IDLHs derived for the SCP were set at

\* The definitions for *toxic* and *highly toxic* also include LD<sub>50</sub> (median lethal dosage) criteria for mortality by ingestion and contact. LD<sub>50</sub> values generally are not determined for or applicable to gases and volatile substances, such as refrigerants, since the standard test methods are not suited for them. Similarly, the likelihood of ingestion of or prolonged contact with the quantities involved is remote. Some LD<sub>50</sub> data, mostly based on solutions of refrigerants in liquids, are provided in reference 20.

100% of the lower-flammability limit (LFL), if there were no known health hazards below those concentrations, the 1994 IDLHs are reduced to 10% of the LFL. Most fire codes use the IDLH, based on the SCP definition, as a criterion for ventilation rates and emergency discharge treatment. Standard 15 also uses the SCP IDLH as one of several criteria to determine refrigerant quantity limits for occupied areas. Use of the IDLH concentrations for these purposes has been challenged as inconsistent with their definition.

**PEL:** The "permissible exposure limit" is the concentration level established by the Occupational Safety and Health Administration (OSHA). Without qualification, the PEL implies a time weighted average (TWA) for an 8-hour work shift in a 40-hour work week. Consistent data include similarly-defined occupational exposure limits set by manufacturers (such as the Allowable Exposure Limit, AEL), the Threshold Limit Value (TLV) adopted by the American Conference of Governmental Industrial Hygienists (ACGIH),<sup>16</sup> and the Workplace Environmental Exposure Level (WEEL) guides developed by the American Industrial Hygiene Association (AIHA).<sup>17</sup> Where designated as a PEL-C (e.g., for R-11), the PEL is a ceiling concentration that shall not be exceeded. Most codes use either PEL or TLV-TWA values as the maximum activation levels for leak-detector alarms; Standard 15 and the new International Mechanical Code (IMC) use the TLV-TWA. While the PEL and TLV-TWA are similarly defined, and the original PELs were based on TLVs, the PEL values have not been revised since 1971. More protective limits published in 1989 were vacated by a court order in 1992. ACGIH publishes annual TLV updates. Still, neither PELs nor TLVs have been set for most alternative refrigerants, for which the primary recourse is use of WEELs or other consistent measures.

**UL group:** The Underwriters Laboratories classification reflects the comparative life hazard of refrigerants in the absence of flames or surfaces at high temperatures. Group 1 is the most toxic (e.g., R-764) and group 6 the least.<sup>18</sup> This measure is used to classify refrigerants in older codes, still in effect in some jurisdictions.

**Standard 34 safety group:** This classification consists of a letter (A or B), which indicates the toxicity class, followed by a number (1, 2, or 3), which indicates the flammability class. Toxicity classes A and B signify refrigerants with *lower toxicity* and *higher toxicity*, respectively, based on prescribed measures of chronic (long-term, repeated exposures) toxicity. Flammability class 1 indicates refrigerants that do not show flame propagation in air when tested by prescribed methods at specified conditions. Classes 2 and 3 signify refrigerants with *lower flammability* and *higher flammability*, respectively; the distinction depends on both the LFL and heat of combustion (HOC). Some of the mechanical codes written before 1993 used an older safety classification system from earlier editions of Standard 34. They included groups 1 (no flame propagation and low degree of toxicity), 2 (TLV-TWA less than 400 ppm), 3a (flammable with low LFL or high HOC), 3b (flammable with high LFL and low HOC), 4a (mixtures of groups 1 and 3a that are nonflammable as formulated, but could become flammable upon fractionation), and 4b (mixtures of groups 1 and 3b that are nonflammable as formulated, but could become flammable upon fractionation). Excluding the group 2 refrigerants, the ranked order from the lowest to highest flammability hazard was 1, 4b, 4a, 3b, and 3a. One motive for the current classification system, introduced in 1992, was to provide a more rational system. Based on current understanding and usage, however, the author questions whether two toxicity classes provide sufficient distinction and whether the classification criterion should be a measure of acute, rather than chronic, toxicity or a combination of acute and chronic toxicity.

**quantity limits for occupied areas:** The primary criterion to determine whether refrigeration systems, or refrigerant-containing components, are allowed in occupied areas of buildings are quantity limits set by the codes or Standard 15. Nearly all limits set in the codes were transcribed from Standard 15, though a few intended and unintended revisions were made in the process.

As discussed above, efforts are underway to develop consensus quantity limits for new refrigerants, including blends. The following additional data are likely to be needed:

**cardiac sensitization:** An acute effect in which the heart is rendered more sensitive to the body's own catecholamine compounds or administered drugs, such as epinephrine, possibly resulting in irregular heart beat (cardiac arrhythmia), which could be fatal.<sup>10</sup> **LOEL** is the "lowest-observed effect level," the lowest concentration at which sensitization occurs in tests, normally to beagle dogs treated with epinephrine to simulate the effects of stress. **NOEL** is the "no-observed effect level," the highest exposure concentration at which no sensitization is observed.

**anesthetic EC<sub>50</sub>:** The concentration of a substance that caused the temporary loss of ability to perceive pain and other sensory stimulation to 50% of test animals, normally measured for 10 minute exposures. **EC<sub>50</sub>** refers to the "effective concentration for 50% of specimens."

**RD<sub>50</sub>:** The concentration that resulted in 50% decrease in respiratory rate, normally measured in mice. A maximal effect generally occurs in less than 30 minutes; the response to R-717 (ammonia), as an example, is reported to take approximately two minutes.

**Table 1: Refrigerant Toxicity Data, Exposure Limits, and Classifications** <sup>a</sup> (data and limits in ppm v/v)

refrig erant- <sup>b</sup>	LC <sub>50</sub> <sup>c</sup>	cardiac sensitization <sup>d</sup>		anes- thetic EC <sub>50</sub> <sup>e</sup>	RD <sub>50</sub> <sup>f</sup>	IDLH <sup>g</sup>		PEL <sup>h</sup>	UL <sup>i</sup> group	safety group <sup>b</sup>
		LOEL	NOEL			SCP	1994			
11	26 200	5 000	1 100	35 000	--	5 000 <sup>j</sup>	2 000	C1 000 <sup>j</sup>	5(a)	A1
12	>800 000	50 000	25 000	250 000	--	50 000	15 000	1 000	6	A1
22	220 000	50 000	25 000	140 000	--	50 000 <sup>k</sup>	--	1 000 <sup>l</sup>	5(a)	A1
23	>663 000	>800 000	300 000	186 000 <sup>m</sup>	--	--	--	1 000 <sup>k</sup>	6 <sup>k</sup>	A1
32	>760 000 <sup>n</sup>	250 000	200 000	86 000 <sup>m</sup>	--	--	--	1 000 <sup>p</sup>	--	A2
113	52 000 <sup>n</sup>	5 000	2 500	28 000	--	4 500	2 000	1 000	4-5	A1
114	>600 000 <sup>o</sup>	25 000	--	250 000	--	50 000	15 000	1 000	6	A1
115	>800 000 <sup>n</sup>	150 000	--	28 000 <sup>m</sup>	--	--	--	1 000 <sup>l</sup>	6	A1
116	>800 000 <sup>n</sup>	<sup>q</sup>	200 000	800 000 <sup>m</sup>	--	--	--	1 000 <sup>k</sup>	6 <sup>k</sup>	A1
123	32 000	20 000	10 300	40 000	--	4 000 <sup>k</sup>	--	10-30 <sup>k</sup>	--	B1
124	262 500	25 000	10 000	140 000	--	--	--	1 000 <sup>p</sup>	6	A1
125	>800 000 <sup>n</sup>	100 000	75 000	>10 000 <sup>m</sup>	--	--	--	1 000 <sup>p</sup>	--	A1
134a	567 000 <sup>n</sup>	75 000	50 000	205 000 <sup>m</sup>	--	50 000 <sup>k</sup>	--	1 000 <sup>p</sup>	--	A1
141b	61 647	5 000	2 500	25 000	--	--	--	500 <sup>p</sup>	--	--
142b	128 000 <sup>n</sup>	50 000	25 000	250 000	--	--	--	1 000 <sup>p</sup>	--	A2
143a	>540 000 <sup>n</sup>	300 000	250 000	>540 000 <sup>m</sup>	--	--	--	1 000 <sup>p</sup>	--	A2
152a	383 000 <sup>n</sup>	150 000	50 000	200 000	--	--	--	1 000 <sup>p</sup>	--	A2
218	>800 000 <sup>o</sup>	400 000	300 000	>113 000 <sup>m</sup>	--	--	--	1 000 <sup>p</sup>	--	A1
290	>800 000 <sup>o</sup>	100 000	50 000	280 000	--	20 000 <sup>r</sup>	2 100	1 000	5(b)	A3
C318	>800 000	100 000	--	>600 000 <sup>m</sup>	--	--	--	--	6 <sup>k</sup>	A1
600	280 000	5 000	--	130 000	--	--	--	800 <sup>l</sup>	5(b)	A3
600a	570 000 <sup>o</sup>	50 000	25 000	200 000 <sup>s</sup>	--	--	--	600 <sup>k</sup>	5(b)	A3
717	2 000 <sup>t</sup>	--	--	--	303	500	300	50 <sup>u</sup>	2	B2
744	<sup>v</sup>	--	--	--	--	50 000	40 000	5 000	5(a)	A1
1270	650 000 <sup>w</sup>	100 000	--	400 000	--	--	--	1 000 <sup>k</sup>	--	A3

<sup>a</sup> Please see the source publications (identified in reference 20) to verify these data and examine their limitations.

<sup>b</sup> from ANSI/ASHRAE Standard 34-1992 and addenda thereto

<sup>c</sup> 4-hr LC<sub>50</sub> rat; federal and fire code toxicity classifications are based on a 1-hr LC<sub>50</sub> rat

<sup>d</sup> dog with epinephrine challenge

<sup>e</sup> 10-min EC<sub>50</sub> mouse or rat

<sup>f</sup> 30-min RD<sub>50</sub> mouse

<sup>g</sup> NIOSH IDLH values from the Standards Completion Program (SCP) and 1994 revision<sup>13</sup>

<sup>h</sup> time-weighted average (TWA) for 8 hr/day and 40 hr/wk

<sup>i</sup> comparative life hazard where group 1 is the most toxic and group 6 the least

<sup>j</sup> The SCP IDLH and OSHA PEL are 10 000 and 1 000 ppm, respectively; ARI recommends 5 000 and C1 000 ppm based on the cardiac sensitization potential.<sup>19</sup>

<sup>k</sup> industry or manufacturer recommendation

<sup>l</sup> ACGIH Threshold Limit Value - Time-Weighted Average (TLV-TWA)<sup>16</sup>

<sup>m</sup> anesthetic effects observed in rats at this concentration during ALC, LC<sub>50</sub>, or other studies

<sup>n</sup> 4-hr Approximate Lethal Concentration (ALC) rat

<sup>o</sup> 2-hr LC<sub>50</sub> rat for R-114; 1-hr ALC rat for R-218; and 15-min LC<sub>50</sub> rat for R-290 and R-600a<sup>17</sup>

<sup>p</sup> AIHA Workplace Environmental Exposure Limit (WEEL)

<sup>q</sup> response observed at 200 000 ppm in anesthetized dogs using tracheal cannulae (intubation); no effect found at 600 000 ppm, in a separate study, by simple inhalation

<sup>r</sup> based on the lower flammability limit (LFL)

<sup>s</sup> 17-min EC<sub>50</sub> mouse

<sup>t</sup> wide dispersion found in the literature: 6 586 - 19 671 for 1 hr and 2 000 - 4 067 for 4 hr

<sup>u</sup> ACGIH Threshold Limit Value - Time-Weighted Average (TLV-TWA) = 25 ppm

<sup>v</sup> 5-min LC<sub>L0</sub> human = 90 000 ppm

<sup>w</sup> 2-hr ALC rat (4-hr ALC rat ≈ 460,000 ppm using the conversion from reference 11)

Working drafts of the proposed method to determine quantity limits, identified as Recommended Quantity Limits (RQLs), use the preceding acute-toxicity data to determine an intermediate limit, identified as the Acute Toxicity Exposure Limit (ATEL). The RQL is then set at the lowest of the ATEL, the oxygen deprivation level (ODL, the calculated concentration that will reduce the oxygen concentration in normal air to below 19½% by volume) of 69 100 ppm, and 25% of the LFL. One proposal to establish RQLs for blends uses the same calculation method as for single compounds, after determining a mole-weighted average for each parameter based on the values for the blend components.

## **Findings**

Table 1 summarizes data for common, single-compound refrigerants. The quantity limits for occupied areas are not included, since the calculation method still is being revised. Those limits and corresponding data and limits for blends will be presented in a subsequent paper.

Multiple values were located for approximately half of the data in the table. In general, those shown are the most conservative found in the published literature, except that the highest published concentrations are included for no-effect levels and where a study found a lower bound to, but did not actually establish, an end point. Space limitations in this paper prevent inclusion of the more than 200 pertinent references from which the data in table 1 were obtained. Specific or multiple corroborating sources and additional data are identified in reference 20.

Comparison of the acute-toxicity data for R-123 to those for R-11 show it to be as safe, or safer, with respect to acute toxicity. The same conclusion results from comparison of the data for R-134a to those for R-12. An earlier paper showed that chronic exposures can be maintained well below recommended limits.<sup>2</sup>

Another point that is evident with the assembled data is that the hydrocarbons proposed as replacements for fluorochemicals are generally more toxic. The LC<sub>50</sub> values for R-32, R-125, R-134a, R-290 (propane), R-600 (butane), R-600a (isobutane), and R-1270 (propene) all indicate very low acute toxicity. The cardiac sensitization and anesthetic effect indicators, however, suggest that R-600 and R-600a pose higher risks than R-134a and that the inhalation lethality of R-1270, while very low, is higher than for either R-32 or R-125. Although not addressed herein, these hydrocarbons also introduce much higher explosivity, flammability, and heat release concerns.

The compiled data result from a fairly extensive data search. Two caveats accompany the data presented. First, the table constitutes a work in progress, to provide data for interim use. Some of the values may be superseded as further information is located or new data become available. Second, users must satisfy themselves with the suitability and appropriateness of the data for specific uses. The data or resultant determinations also must be approved by the code official having jurisdiction where required. While care has been taken in assembly of the data, the effort cannot be viewed as exhaustive and no attempt was made to verify the data. They are intended for use by knowledgeable professionals, and offered without warranty of any kind.

## **Additional Data Sources**

Other sources for the data include the PAFT summaries<sup>5</sup> published scientific literature, manufacturers, and material safety data sheets. A number of databases are available to assist in finding the data, among them the Chemical Abstract Service (CAS), Hazardous Substances Data Base (HSDB), and Registry of Toxic Effects of Chemical Substances (RTECS). Additional sources, including a number of compilations, are identified in reference 20.

## **CONCLUSIONS**

The toxicity data presented herein provide an interim means to address code requirements for use of alternative refrigerants, subject to the caveats indicated. These data also may be useful to evaluate proposed changes to safety standards for refrigerants and refrigeration. While the data show the alternative refrigerants to be of comparable or lower toxicity than those they replace, and especially so for acute effects, safe use depends on adherence to proper application, handling, and service procedures.

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